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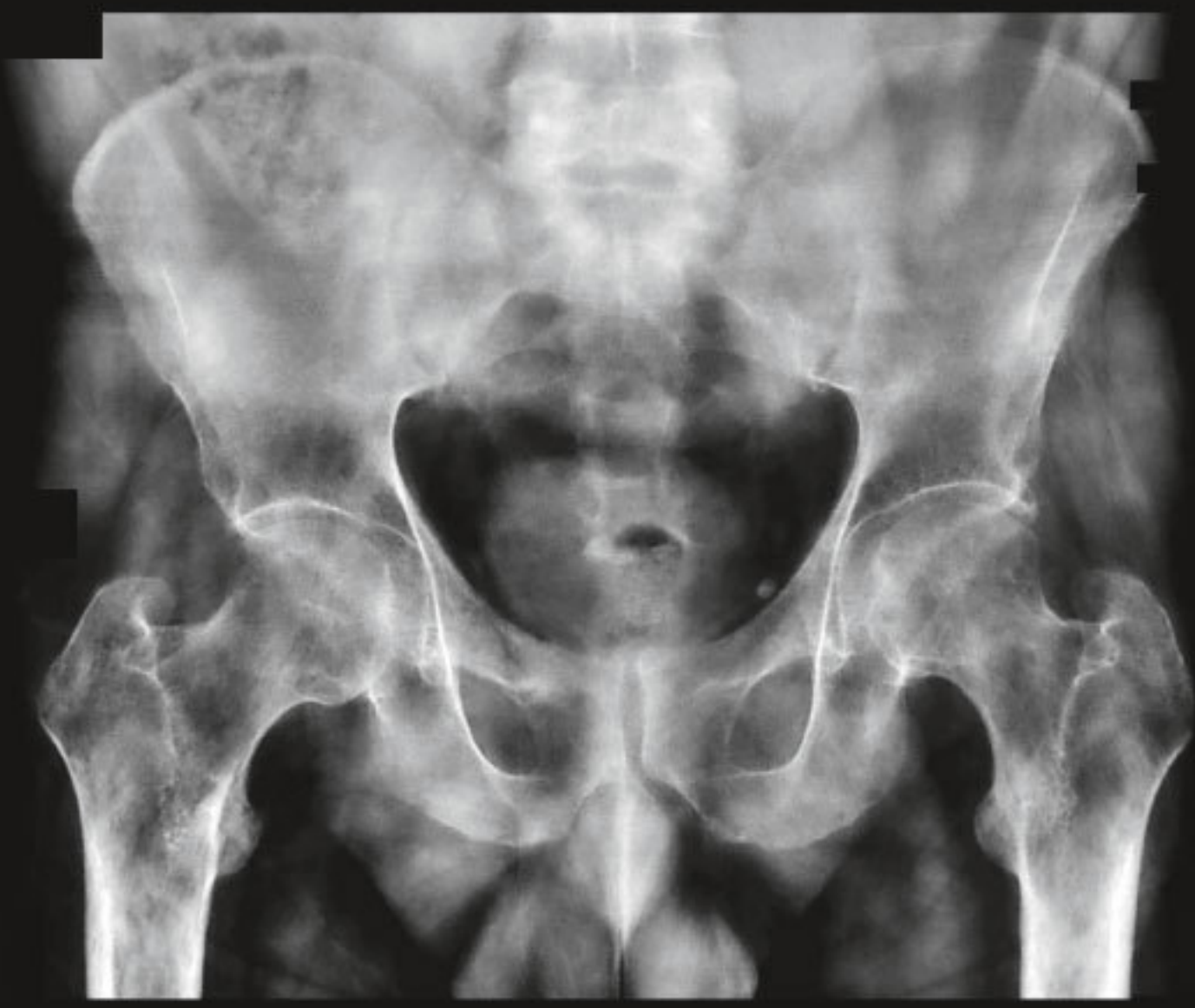

Arthritis Care & Research

Aims and Scope

Arthritis Care & Research is an official journal of the American College of Rheumatology and the Association of Rheumatology Professionals, a division of the College. *Arthritis Care & Research* is a peer-reviewed journal that publishes both original research and review articles that promote excellence in the clinical practice of rheumatology. Relevant to the care of individuals with arthritis and related disorders, major topics are evidence-based practice studies, clinical problems, practice guide-lines, health care economics, health care policy, educational, social, and public health issues, and future trends in rheumatology practice.

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Cover image: The figure on the cover (from Abi-Ghanem et al, page 2) is a plain radiograph of the pelvis showing prominent diffuse osseous demineralization and cortical thinning. The patient is a 49-year-old man presenting with a 2-year history of debilitating diffuse joint, muscle, and bone pain.

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CLINICOPATHOLOGIC CONFERENCE

A 49-Year-Old Man With Debilitating Aches and Pains and a Mysterious Culprit

Alain S. Abi-Ghanem,[1] Camil J. Chouairy,[2] Zarouhie Meguerian,[2] and Lama Azar[2]

CASE PRESENTATION

Chief symptoms

A 49-year-old man presented with a 2-year history of debilitating diffuse joint, muscle, and bone pain.

History of present illness

The patient reported pain that started insidiously in his feet and gradually progressed proximally from the lower extremities to the pelvis, spine, and chest. He described it as dull, aching, and constant and exacerbated by minimal movement and even inspiration. He complained of frequent severe muscle spasms, cramps, progressive weakness, and difficulty with ambulation leading to the use of a wheelchair. He also reported being diagnosed as having multiple nontraumatic rib fractures. The patient had seen many physicians in the past for his condition and was given a multitude of treatments without effect. Nonsteroidal antiinflammatory medications provided minimal relief, and treatments with oral sulfasalazine (2 gm daily), golimumab (50 mg subcutaneously once per month for 6 months), and then etanercept (50 mg subcutaneously once per week for 6 months) for presumed spondyloarthritis had no effect. He was diagnosed as having fibromyalgia by other physicians and was prescribed pregabalin treatment without improvement. He denied using any other medications.

Past medical history

The patient had a history of latent tuberculosis treated with a 6-month course of isoniazid 3 years prior to presentation. His past medical and surgical history were otherwise unremarkable.

Social and family history

The patient had no history of tobacco, alcohol, or illicit drug use, as well as no recent travel or contact with other people who were sick. He had lost his job in sales and distribution in a supermarket due to his illness. He had no known family history of autoimmune, neuromuscular, or metabolic bone diseases.

Review of systems

Additional symptoms, including fever, night sweats, weight loss, oral ulcers, rashes (such as psoriasis, palmoplantar pustulosis, or severe acne), dry eyes or dry mouth, red or painful eye, cough, dyspnea, dysphagia, abdominal pain, diarrhea or red blood per rectum, paresthesias, and bladder or bowel dysfunction, were absent.

Physical examination

Upon examination, the patient appeared in significant distress due to pain. He had difficulty transferring from his wheelchair to the examination table and was unable to bear weight unaided. A waddling gait was noted. His vital signs were normal. He was alert and oriented to person, place, and time. His speech was normal and appropriate. The skin was intact. Pupils were equally round and reactive to light and accommodation. The sclera, conjunctiva, oral, and nasal mucosa were normal, as was the tongue and gums. The thyroid was not enlarged, and the lungs were clear to auscultation. The patient had a normal and regular heart rate and rhythm. No abnormal heart sounds, murmurs, or rubs were appreciated. Distal pulses were normal. The abdomen was soft and nontender, and no organomegaly was noted. He had no palpable nodes in the cervical, supraclavicular, axillary, or inguinal areas.

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No potential conflicts of interest relevant to this article were reported.

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The musculoskeletal examination revealed normal spinal curvatures, and no deformities of the joints were noted. He had severe tenderness to palpation of bones, especially over the spinous processes, ribs, and long bones of the lower extremities bilaterally. The FABER test (hip Flexion, Abduction, and External Rotation) showed negative results. The patient had full and symmetrical passive range of motion of his joints with no evidence of synovitis.

The neurologic examination revealed intact cranial nerves II–XII and coordination, as evaluated by rapid alternating movements and finger-to-nose testing. No involuntary movements were noted, including no tremors or myoclonus. The patient had no pronator drift, and muscle bulk and tone were normal. No fasciculations were noted. His motor strength was 4/5 bilaterally in the hip flexor, extensor, abductor, and adductor muscles. The rest of his motor examination was normal. The biceps, triceps, brachioradialis, patellar, and Achilles deep tendon reflexes were normal, and he had a plantar flexor response. Sensory examination findings, including light touch, pain, vibration, and 2-point discrimination, were normal.

Initial laboratory evaluation

Results of the initial laboratory evaluation are shown in Table 1. These results were unremarkable except for a low fasting serum phosphorus level of 1.3 mg/dl, an elevated alkaline phosphatase level 5 times the upper limit of normal, an elevated parathyroid hormone (PTH) level (90 pg/ml [normal range 10–65]), and low 1,25-dihydroxyvitamin D (12 ng/liter [normal range 18–71]).

Radiographic evaluation

Plain radiography of the pelvis (Figure 1) showed prominent diffuse osseous demineralization and cortical thinning. There was no evidence of sacroiliitis, cortical thickening, sclerosis, osseous deformity, or periostitis.

CASE SUMMARY

The patient is a 49-year-old man presenting with a 2-year history of debilitating diffuse bone pain and tenderness, proximal lower extremities weakness, and a waddling gait. His examination findings showed significant hypophosphatemia with high PTH and alkaline phosphatase levels, low 1,25-dihydroxyvitamin D, and diffuse demineralization on imaging.

DIFFERENTIAL DIAGNOSIS

The above clinical presentation and laboratory findings suggest the following disorders: primary hyperparathyroidism, Paget's disease of bone, multiple myeloma, and osteomalacia.

Table 1. Laboratory results*

	Value	Normal range
WBC count, cells/mm^3	10	4–10
Hemoglobin, gm/dl	15.4	13–17
Platelet count, cells/mm^3	179	150–400
Sodium, mmoles/liter	145	135–145
Potassium, mmoles/liter	3.8	3.5–5
Chloride, mmoles/liter	105	95–105
CO_2, mmoles/liter	23	22–29
Creatinine, mg/dl	0.62	0.6–1.2
Glucose, mg/dl	102	70–110
Albumin, gm/dl	4.8	3.5–5
Calcium, mg/dl	10.1	8.4–10.2
Phosphorus, mg/dl	1.3	3–4.5
Magnesium, mg/dl	2	1.3–2.1
Aspartate aminotransferase, units/liter	15	<40
Alanine aminotransferase, units/liter	43	<42
Alkaline phosphatase, units/liter	625	40–129
Gamma glutamyl transpeptidase, units/liter	37	8–61
Total bilirubin, mg/dl	0.64	<1.2
Creatine kinase, units/liter	19	39–308
Thyroid-stimulating hormone, µU/liter	2.1	0.4–5
CRP level, mg/liter	4.1	<10
ESR, mm/hour	15	0–20
25-hydroxyvitamin D, ng/ml	27	30–70
1,25-hydroxyvitamin D, ng/l	12	18–71
Parathyroid hormone, pg/ml	90	10–65

* WBC = white blood cell; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate.

Primary hyperparathyroidism

The patient's bone pain presentation, the elevated PTH level at 90 pg/ml (normal range 10–65), hypophosphatemia, and diffuse demineralization on radiographs suggestive of

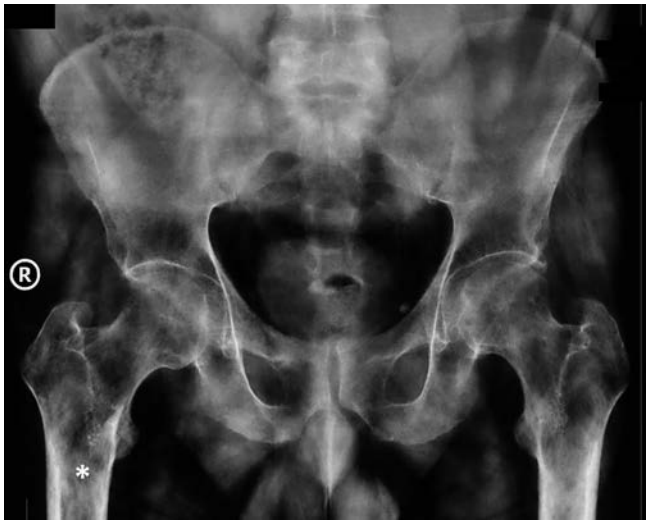

Figure 1. Plain radiograph of the patient's pelvis showing prominent diffuse osseous demineralization and cortical thinning (**asterisk**). R = right.

osteoporosis raise the possibility of primary hyperparathyroidism. The classic manifestation of primary hyperparathyroidism bone disease, osteitis fibrosa cystica, is rare. However, the patient's serum calcium level, confirmed twice, was normal, making the possibility of osteitis fibrosa cystica unlikely. Moreover, the other abnormal laboratory test results associated with hyperparathyroidism such as hypomagnesemia and elevated 1,25-dihydroxyvitamin D were absent (1). Most patients with normocalcemic primary hyperparathyroidism are asymptomatic (2,3). Therefore, the elevated PTH in this case is more likely to be explained by secondary hyperparathyroidism. In the absence of renal failure, significant 25-hydroxyvitamin D deficiency, and malabsorptive disorders, one plausible cause is the low calcitriol level, the etiology of which needed to be explored (4).

Paget's disease of bone

Paget's disease of bone is a focal disorder of bone metabolism that occurs in the aging skeleton and is characterized by accelerated bone turnover and disorganized bone remodeling, leading to abnormal bony overgrowth. Its onset is usually after the age of 55 years, and it affects slightly more men than women. Many patients are asymptomatic, and the diagnostic clues are often a rising serum alkaline phosphatase level and/or an incidental finding of characteristic radiographic changes such as cortical thickening, expansion, coarsening of the trabecular markings, and mixed areas of lucency and sclerosis (5,6). In this case, the possibility of Paget's disease of bone was raised in view of the bone pain presentation and the elevated alkaline phosphatase level. The young age of the patient, the presence of hypophosphatemia, and the absence of the characteristic radiographic findings of Paget's disease of bone present arguments against this diagnosis.

Multiple myeloma

Multiple myeloma is characterized by the neoplastic proliferation of immunoglobulin-producing plasma cells. Weakness, fatigue, and bone pain, particularly of the back and chest, are commonly reported by patients with this disease (7). It is also associated with decreased bone density and fractures (8). Hypophosphatemia may occur in the setting of multiple myeloma associated with proximal tubular dysfunction (Fanconi syndrome) (9). Moreover, spurious hypophosphatemia has been described in patients with multiple myeloma (10,11). However, the other common findings of multiple myeloma, such as anemia, hypercalcemia, and renal impairment, were absent in this case. The patient's significantly elevated alkaline phosphatase level is uncommon in multiple myeloma, and the patient had no characteristic punched-out lytic lesions on the radiograph of the pelvis.

Table 2. Major causes of osteomalacia (12,34,54–65)

Abnormal vitamin D metabolism
Low vitamin D dietary intake
Insufficient sunlight exposure
Gastrointestinal malabsorption
Liver disease
Anticonvulsant use
Hypoparathyroidism
Renal failure
Vitamin D–dependent rickets type 1 and 2
Hypophosphatemia
Decreased intestinal phosphorus absorption
Low phosphorus dietary intake
Antacids
Vitamin D deficiency or resistance
Renal phosphorus wasting
Hereditary hypophosphatemic rickets
Fanconi syndrome
Multiple myeloma
Tumor-induced osteomalacia
Mineralization defects
Chronic renal failure
Osteogenesis and fibrogenesis imperfecta
Aluminum, fluoride
Hypophosphatasia

Osteomalacia

Osteomalacia is a metabolic bone disease characterized by a defective mineralization of newly formed osteoid at sites of bone turnover (12,13). Patients usually present with bone pain and tenderness, muscle weakness, difficulty walking, and a waddling gait. These are relatively vague, nonspecific symptoms and, not unusually, patients are misdiagnosed as having a variety of other rheumatologic or neuropsychiatric conditions such as spondyloarthritis, polymyalgia rheumatica, myopathies, fibromyalgia, and conversion disorders (14–20). A high degree of suspicion in the right clinical context is necessary to make this diagnosis, especially in the earliest stages of the disease. Several different disorders cause osteomalacia by one of the following mechanisms: abnormal vitamin D metabolism, mineralization defects, and hypophosphatemia (Table 2). In view of the laboratory findings in the present case, hypophosphatemia-related osteomalacia needs to be considered first.

CLINICAL COURSE

Findings from the serum protein electrophoresis with immunofixation and free kappa and lambda chains levels were normal, thereby excluding a diagnosis of multiple myeloma. The striking laboratory finding in this case was the hypophosphatemia. The patient's medical history, examination findings, and laboratory test results did not reveal a cause of decreased intestinal phosphorus absorption such as inadequate dietary intake, malabsorptive disorders, antacid use, or severe vitamin D deficiency. Therefore, renal phosphate wasting was suspected. This was confirmed by an inappropriately low renal tubular reabsorption of

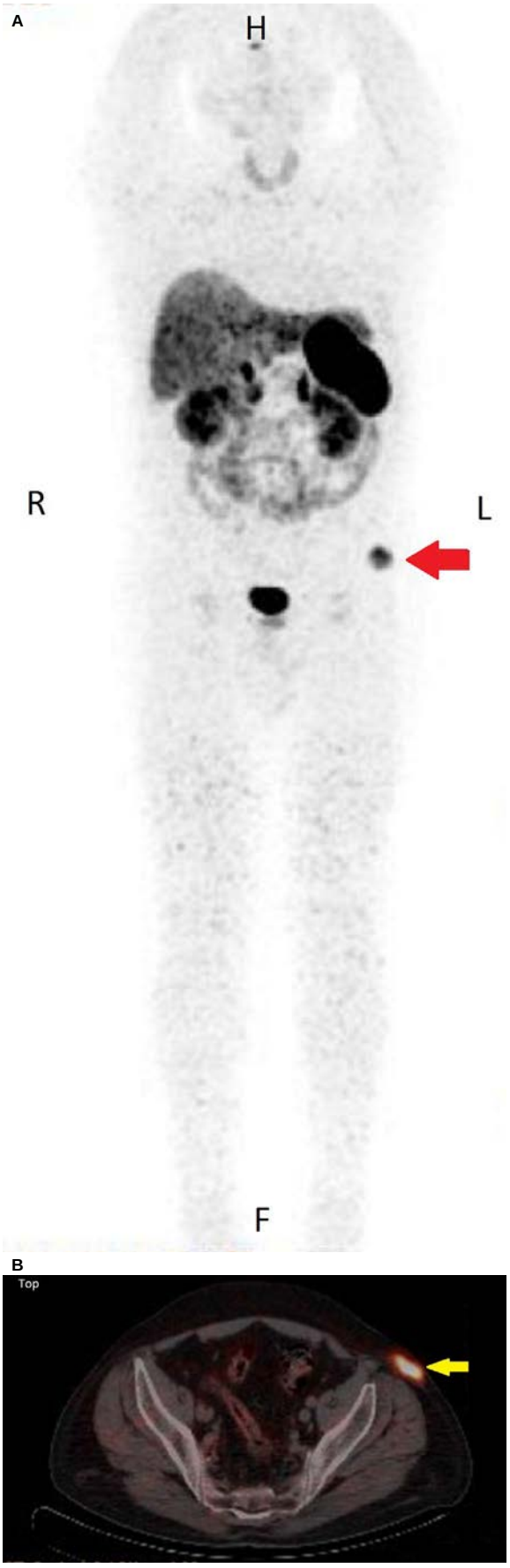

Figure 2. Image showing ^{68}Ga-DOTATOC whole-body positron emission tomography (PET)/computed tomography (CT) with maximum intensity projection (top) and axial fused PET/CT at the level of the pelvis (bottom). Both top and bottom figures show a 4.5 × 1.7–cm intensely radiotracer-avid subcutaneous soft tissue mass in the left anterior pelvic wall with SUVmax 8.9 (**arrows**). Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/acr.23807/abstract.

phosphate (TRP) at 64% (%TRP = 100 × [1 – ([urine phosphate/urine creatinine] × [serum creatinine/serum phosphate])]). When phosphate is normal, %TRP is expected to be between 85% and 95%. Similarly, the patient's renal tubular maximum reabsorption of phosphorus corrected for glomerular filtration rate was inappropriately low at 0.83 mg/dl (normal range for age and sex 2.78–4.18). This means that the maximum tubular reabsorption of phosphorus was lower than expected for the patient's low serum phosphorus concentration, confirming renal phosphate wasting as the etiology of his hypophosphatemia (21,22). Therefore, the diagnosis of hypophosphatemia-related osteomalacia appears the most likely. From among the causes of hypophosphatemia-related osteomalacia, as listed in Table 2, the following 2 conditions best explained the patient's presentation: tumor induced osteomalacia (TIO) and hereditary hypophosphatemic rickets.

TIO

Also known as oncogenic osteomalacia, TIO is a rare disorder caused by the secretion of fibroblast growth factor 23 (FGF-23) by benign mesenchymal tumors. FGF-23 acts primarily at the renal tubule by impairing phosphate reabsorption and 1α-hydroxylation of 25-hydroxyvitamin D, therefore leading to decreased mineralization of newly formed bone and the clinical

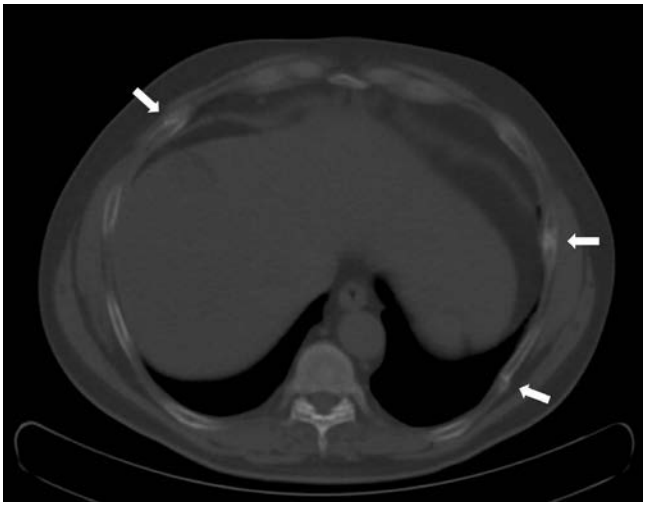

Figure 3. Axial computed tomography image of the lower chest showing several healing fractures of the rib with callus formation (**arrows**).

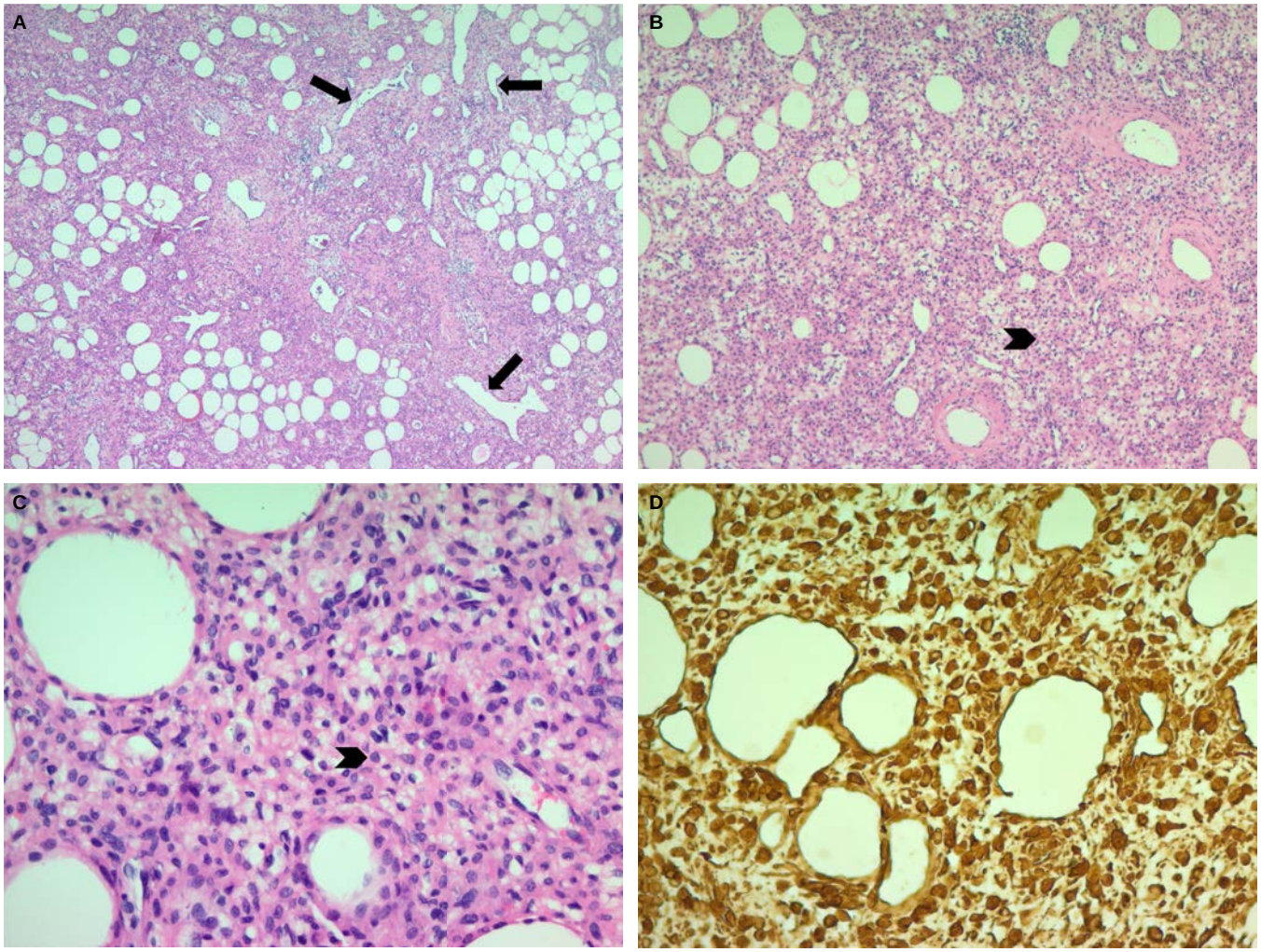

Figure 4. **A**, Hematoxylin and eosin (H&E)–stained cells (original magnification × 25) showing almost equal amounts of adipose tissue and mesenchymal cells. Note the thin-walled blood vessels with a hemangiopericytoma-like architecture (**arrows**). **B**, H&E-stained cells (original magnification × 50) showing the mesenchymal cells (**arrow**) predominating over the adipocytes in this field. Blood vessels display a thick wall. **C**, H&E-stained cells (original magnification × 200) showing benign mature adipocytes and intimately admixed, round-to-plump mesenchymal cells (**arrow**). **D**, Immunohistochemical stain showing strong diffuse expression of vimentin (original magnification × 200).

findings of osteomalacia and hypophosphatemia (21,23–26). Few studies have addressed the epidemiology of TIO. It typically occurs in adults (mean age 45 years) and affects men and women equally. The time from onset of symptoms to a correct diagnosis often exceeds 2.5 years (27). This delay in diagnosis is probably due to the occult nature of the disease and because the hypophosphatemia, which is the hallmark of TIO, may be overlooked or uninvestigated.

The first person to recognize the association between a tumor, a phosphaturic substance, and a clinical syndrome of osteomalacia was Andrea Prader in 1959 (28). Since that time, ~400 cases have been reported in the literature (21,24,29). A growing recognition of TIO paralleled the identification, in 2000, of FGF-23 as the phosphaturic agent (30,31). The primary challenge in diagnosing TIO is the difficulty, in certain instances, in localizing the tumors due to their small size and obscure locations such as bone and soft tissue. Definitive treatment of the disease is complete tumor resection whenever possible.

Hereditary hypophosphatemic rickets

Hereditary forms of hypophosphatemia or hypophosphatemic rickets refer to several genetic disorders characterized by renal phosphate wasting due to mutations in 1 of the genes that control renal phosphate reabsorption. The most common form, the X-linked hypophosphatemic rickets (XLH), is a dominant disorder due to mutations in the *PHEX* gene, which encodes an enzyme that normally degrades FGF-23. Both boys and girls may be affected. In the absence of familial history, children typically come to medical attention with slowed growth and legs bowing. Craniosynostosis and other craniofacial anomalies may be present. Other clinical presentations in untreated adults

may include weakness, fatigue, bone pain, gait abnormalities, early osteoarthritis, enthesopathy, hearing loss, tinnitus, dental abscesses, and early loss of dentition due to abnormal mineralization of dentin (32–36). In addition to hypophosphatemia, renal phosphate wasting, and high FGF-23 levels, untreated patients with XLH usually have normal serum levels of calcium, normal-to-high PTH and alkaline phosphatase levels, normal plasma 25-vitamin D concentrations, and normal or slightly reduced plasma 1,25-dihydroxyvitamin D concentrations due to increased catabolism and decreased formation of the enzyme (37). The other forms of hereditary hypophosphatemic rickets are rare and include autosomal dominant and autosomal recessive diseases, as well as hypophosphatemic rickets with hypercalciuria.

Consequently, we tested the patient for an FGF-23 level, which showed to be abnormally elevated (350 ng/liter [normal <50]) as seen in TIO and hereditary hypophosphatemic rickets. Given the evidence of this case, TIO is the more likely diagnosis in view of the adult age of onset of the disease, the severity of the presentation, the prominent muscle weakness, and the unrevealing family history.

The next task was to localize the potential tumor. Somatostatin receptor (SSTR) imaging has been proven beneficial in detecting tumors causing TIO since they variably express the 5 SSTRs, allowing SSTR-based functional imaging by octreotide scintigraphy. In the literature, there are several reports of scintigraphy using ^{111}In- and ^{99m}Tc-labeled octreotide (38–44). This imaging modality is limited by 2-dimensional planar imaging and a relatively poor spatial resolution, which is particularly challenging because TIO tumors can be very small in size, arise in bone or soft tissue, and occur from head to toe.

SSTR imaging can now be performed with positron emission tomography (PET)/computed tomography (CT) imaging. Many authors have reported successful tumor localization in TIO using analogs of octreotide labeled with ^{68}Ga (45–50). This patient underwent ^{68}Ga DOTA^{0}-Ty^{3} octreotide (^{68}Ga-DOTATOC) PET/CT imaging that showed a 4.5 × 1.7–cm intensely radiotracer-avid subcutaneous soft tissue mass in the left anterior pelvic wall with SUVmax 8.9 (Figure 2). There were also several non–gallium-avid rib fractures (Figure 3) and mild diffuse cortical erosions involving the right clavicle and lower extremities that were attributed to osteomalacia.

The mass was surgically excised. Histologic examination (Figure 4) revealed a well-circumscribed encapsulated nodule composed of benign mature adipocytes and intimately admixed round-to-plump mesenchymal cells that exhibited cytologically bland nuclei and inconspicuous cytoplasm. The mesenchymal cells grew in an infiltrative, dermatofibrosarcoma-like pattern into the subcutaneous fat. Ropy collagen fibers, as seen in a typical spindle cell lipoma, were absent. The ratio of adipocytes to mesenchymal cells was variable across the nodule. Some areas showed a predominance of adipocytes, while others showed almost equal proportions of mesenchymal cells and adipose tissue. Some blood vessels exhibited a thick wall, while others displayed a thin delicate wall with a hemangiopericytoma-like architecture. No osteoclasts, calcifications, or chondromyxoid or osteoid material were noticed. The mesenchymal cells exhibited the following immunoprofile: 1) vimentin: strong diffuse expression; 2) S-100: negative; 3) CD68: positive; and 4) CD34: focal expression. Although these findings may lack some of the classical features described in osteomalacia-associated mesenchymal tumors, such as calcifications, chondroid and osteoid matrix, and osteoclasts, we believe they highlight again the histopathologic heterogeneity of these tumors, which is a frequent cause of their misdiagnosis (51–53). Regardless of the tumor's morphology, the hallmark of the diagnosis of TIO is the association of the tumor with the clinical syndrome of osteomalacia, hypophosphatemia, elevated plasma FGF-23, and its disappearance after tumor resection.

Our patient's illness followed this expected course. Postoperatively, he reported a gradual improvement of his symptoms, with a complete cure at 2 months. His serum phosphorus level was normal (4 mg/dl) when checked 1 month after the surgical removal of his tumor. He was last evaluated 18 months after his surgery, and there was no clinical evidence of recurrence of his disease at the time.

FINAL DIAGNOSIS

Tumor-induced osteomalacia.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Abi-Ghanem had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Abi-Ghanem, Chouairy, Meguerian, Azar.
Acquisition of data. Abi-Ghanem, Chouairy, Meguerian, Azar.
Analysis and interpretation of data. Abi-Ghanem, Chouairy, Meguerian, Azar.

REFERENCES

1. Silverberg SJ, Bilezikian JP. Evaluation and management of primary hyperparathyroidism. J Clin Endocrinol Metab 1996;81:2036–40.
2. Silverberg SJ, Lewiecki EM, Mosekilde L, Peacock M, Rubin MR. Presentation of asymptomatic primary hyperparathyroidism: proceedings of the third international workshop. J Clin Endocrinol Metab 2009;94:351–65.
3. Tordjman KM, Greenman Y, Osher E, Shenkerman G, Stern N. Characterization of normocalcemic primary hyperparathyroidism. Am J Med 2004;117:861–3.
4. Fraser WD. Hyperparathyroidism. Lancet 2009;374:145–58.
5. Kravets I. Paget's disease of bone: diagnosis and treatment. Am J Med 2018;131:1298–303.
6. Seton M. Paget disease of bone: diagnosis and drug therapy. Cleve Clin J Med 2013;80:452–62.

7. Kyle RA, Gertz MA, Witzig TE, Lust JA, Lacy MQ, Dispenzieri A, et al. Review of 1027 patients with newly diagnosed multiple myeloma. Mayo Clin Proc 2003;78:21–33.
8. Eda H, Santo L, David Roodman G, Raje N. Bone disease in multiple myeloma. Cancer Treat Res 2016;169:251–70.
9. Stokes MB, Valeri AM, Herlitz L, Khan AM, Siegel DS, Markowitz GS, et al. Light chain proximal tubulopathy: clinical and pathologic characteristics in the modern treatment era. J Am Soc Nephrol 2016;27:1555–65.
10. Caras JA. Spurious hypophosphatemia associated with multiple myeloma. Endocr Pract 1997;3:135–6.
11. Loghman-Adham M, Walton D, Iverius PH, Deiss A, Knight JA, Cheung AK. Spurious hypophosphatemia in a patient with multiple myeloma. Am J Kidney Dis 1997;30:571–5.
12. Bhan A, Rao AD, Rao DS. Osteomalacia as a result of vitamin D deficiency. Rheum Dis Clin North Am 2012;38:81–91, viii–ix.
13. Peris P. Diagnosis and treatment of osteomalacia by the rheumatologist. Reumatol Clin 2011;7 Suppl 2:S22–7. In Spanish.
14. Bliddal H, Danneskiold-Samsoe B. Chronic widespread pain in the spectrum of rheumatological diseases. Best Pract Res Clin Rheumatol 2007;21:391–402.
15. De Torrente de la Jara G, Pecoud A, Favrat B. Female asylum seekers with musculoskeletal pain: the importance of diagnosis and treatment of hypovitaminosis D. BMC Fam Pract 2006;7:4.
16. Fabbriciani G, Pirro M, Leli C, Cecchetti A, Callarelli L, Rinonapoli G, et al. Diffuse musculoskeletal pain and proximal myopathy: do not forget hypovitaminosis D. J Clin Rheumatol 2010;16:34–7.
17. Garip Y, Dedeoglu M, Bodur H. Osteomalacia mimicking spondyloarthropathy: a case report. Osteoporos Int 2014;25:1983–5.
18. Reginato AJ, Falasca GF, Pappu R, McKnight B, Agha A. Musculoskeletal manifestations of osteomalacia: report of 26 cases and literature review. Semin Arthritis Rheum 1999;28:287–304.
19. Reilly PA. The differential diagnosis of generalized pain. Baillieres Best Pract Res Clin Rheumatol 1999;13:391–401.
20. Teasell RW, Shapiro AP. Misdiagnosis of conversion disorders. Am J Phys Med Rehabil 2002;81:236–40.
21. Chong WH, Molinolo AA, Chen CC, Collins MT. Tumor-induced osteomalacia. Endocr Relat Cancer 2011;18:R53–77.
22. Walton RJ, Bijvoet OL. Nomogram for derivation of renal threshold phosphate concentration. Lancet 1975;2:309–10.
23. Carpenter TO. Oncogenic osteomalacia: a complex dance of factors. N Engl J Med 2003;348:1705–8.
24. Jan de Beur SM. Tumor-induced osteomalacia. JAMA 2005;294: 1260–7.
25. Jonsson KB, Zahradnik R, Larsson T, White KE, Sugimoto T, Imanishi Y, et al. Fibroblast growth factor 23 in oncogenic osteomalacia and X-linked hypophosphatemia. N Engl J Med 2003;348:1656–63.
26. Minisola S, Peacock M, Fukumoto S, Cipriani C, Pepe J, Tella SH, et al. Tumour-induced osteomalacia. Nat Rev Dis Primers 2017;3:17044.
27. Drezner MK. Tumor-induced osteomalacia. In: Primer on the metabolic bone diseases and disorders of mineral metabolism. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 1999. p. xxv, 502.
28. Prader A, Illig R, Uehlinger E, Stalder G. Rickets following bone tumor. Helv Paediatr Acta 1959;14:554–65. In German.
29. Jiang Y, Xia WB, Xing XP, Silva BC, Li M, Wang O, et al. Tumor-induced osteomalacia: an important cause of adult-onset hypophosphatemic osteomalacia in China: report of 39 cases and review of the literature. J Bone Miner Res 2012;27:1967–75.
30. Consortium A. Autosomal dominant hypophosphataemic rickets is associated with mutations in FGF23. Nat Genet 2000;26:345–8.
31. White KE, Jonsson KB, Carn G, Hampson G, Spector TD, Mannstadt M, et al. The autosomal dominant hypophosphatemic rickets (ADHR) gene is a secreted polypeptide overexpressed by tumors that cause phosphate wasting. J Clin Endocrinol Metab 2001;86:497–500.
32. Polisson RP, Martinez S, Khoury M, Harrell RM, Lyles KW, Friedman N, et al. Calcification of entheses associated with X-linked hypophosphatemic osteomalacia. N Engl J Med 1985;313:1–6.
33. Acar S, Demir K, Shi Y. Genetic causes of rickets. J Clin Res Pediatr Endocrinol 2017;9 Suppl 2:88–105.
34. Alizadeh Naderi AS, Reilly RF. Hereditary disorders of renal phosphate wasting. Nat Rev Nephrol 2010;6:657–65.
35. Michalus I, Rusinska A. Rare, genetically conditioned forms of rickets: Differential diagnosis and advances in diagnostics and treatment. Clin Genet 2018;94:103–14.
36. Murthy AS. X-linked hypophosphatemic rickets and craniosynostosis. J Craniofac Surg 2009;20:439–42.
37. Yuan B, Xing Y, Horst RL, Drezner MK. Evidence for abnormal translational regulation of renal 25-hydroxyvitamin D-1alpha-hydroxylase activity in the hyp-mouse. Endocrinology 2004;145:3804–12.
38. Casari S, Rossi V, Varenna M, Gasparini M, Parafioriti A, Failoni S, et al. A case of oncogenic osteomalacia detected by 111In-pentetreotide total body scan. Clin Exp Rheumatol 2003;21:493–6.
39. Jan de Beur SM, Streeten EA, Civelek AC, McCarthy EF, Uribe L, Marx SJ, et al. Localisation of mesenchymal tumours by somatostatin receptor imaging. Lancet 2002;359:761–3.
40. Jing H, Li F, Zhuang H, Wang Z, Tian J, Xing X, et al. Effective detection of the tumors causing osteomalacia using [Tc-99m]-HYNIC-octreotide (99mTc-HYNIC-TOC) whole body scan. Eur J Radiol 2013;82:2028–34.
41. Mendoza Narvaez JA, Bellon Guardia ME, Garcia Vicente AM, Palomar Munoz A, Talavera Rubio MP, Soriano Castrejon AM. Parascapular lipoma with expression of somatostatin receptors detected by (99m)Tc-EDDA/HYNIC-TOC scintigraphy. Rev Esp Med Nucl Imagen Mol 2012;31:225–6. In Spanish.
42. Nguyen BD, Wang EA. Indium-111 pentetreotide scintigraphy of mesenchymal tumor with oncogenic osteomalacia. Clin Nucl Med 1999;24:130–1.
43. Rodrigues NR, Calich AL, Etchebehere M, Ichiki WA, Pereira FP, Amstalden EM, et al. Whole-body (99m)Tc-octreotide scintigraphy with SPECT/CT to detect occult tumor inducing paraneoplastic osteomalacia. Clin Nucl Med 2015;40:54–7.
44. Duet M, Kerkeni S, Sfar R, Bazille C, Liote F, Orcel P. Clinical impact of somatostatin receptor scintigraphy in the management of tumor-induced osteomalacia. Clin Nucl Med 2008;33:752–6.
45. Agrawal K, Bhadada S, Mittal BR, Shukla J, Sood A, Bhattacharya A, et al. Comparison of 18F-FDG and 68Ga DOTATATE PET/CT in localization of tumor causing oncogenic osteomalacia. Clin Nucl Med 2015;40:e6–10.
46. Clifton-Bligh RJ, Hofman MS, Duncan E, Sim Ie W, Darnell D, Clarkson A, et al. Improving diagnosis of tumor-induced osteomalacia with Gallium-68 DOTATATE PET/CT. J Clin Endocrinol Metab 2013;98:687–94.
47. El-Maouche D, Sadowski SM, Papadakis GZ, Guthrie L, Cottle-Delisle C, Merkel R, et al. Ga-DOTATATE for tumor localization in tumor-induced osteomalacia. J Clin Endocrinol Metab 2016;101:3575–81.
48. Zhang J, Zhu Z, Zhong D, Dang Y, Xing H, Du Y, et al. 68Ga DOTATATE PET/CT is an accurate imaging modality in the detection of culprit tumors causing osteomalacia. Clin Nucl Med 2015;40: 642–6.
49. Von Falck C, Rodt T, Rosenthal H, Langer F, Goesling T, Knapp WH, et al. Ga-DOTANOC PET/CT for the detection of a mesenchymal

tumor causing oncogenic osteomalacia. Eur J Nucl Med Mol Imaging 2008;35:1034.

50. Hofmann M, Maecke H, Borner R, Weckesser E, Schoffski P, Oei L, et al. Biokinetics and imaging with the somatostatin receptor PET radioligand Ga-DOTATOC: preliminary data. Eur J Nucl Med 2001;28:1751–7.
51. Agaimy A, Michal M, Chiosea S, Petersson F, Hadravsky L, Kristiansen G, et al. Phosphaturic mesenchymal tumors: clinicopathologic, immunohistochemical and molecular analysis of 22 cases expanding their morphologic and immunophenotypic spectrum. Am J Surg Pathol 2017;41:1371–80.
52. Folpe AL, Fanburg-Smith JC, Billings SD, Bisceglia M, Bertoni F, Cho JY, et al. Most osteomalacia-associated mesenchymal tumors are a single histopathologic entity: an analysis of 32 cases and a comprehensive review of the literature. Am J Surg Pathol 2004;28:1–30.
53. Goldblum JR, Folpe AL, Weiss SW, Enzinger FM, Weiss SW. Enzinger and Weiss's soft tissue tumors. 6th ed. Philadelphia: Saunders/Elsevier; 2014. p. xiv, 1155.
54. Brame LA, White KE, Econs MJ. Renal phosphate wasting disorders: clinical features and pathogenesis. Semin Nephrol 2004;24:39–47.
55. Clarke BL, Wynne AG, Wilson DM, Fitzpatrick LA. Osteomalacia associated with adult Fanconi's syndrome: clinical and diagnostic features. Clin Endocrinol (Oxf) 1995;43:479–90.
56. Forlino A, Marini JC. Osteogenesis imperfecta. Lancet 2016;387:1657–71.
57. Frame B, Frost HM, Pak CY, Reynolds W, Argen RJ. Fibrogenesis imperfecta ossium: a collagen defect causing osteomalacia. N Engl J Med 1971;285:769–72.
58. Fukumoto S, Ozono K, Michigami T, Minagawa M, Okazaki R, Sugimoto T, et al. Pathogenesis and diagnostic criteria for rickets and osteomalacia: proposal by an expert panel supported by the Ministry of Health, Labour and Welfare, Japan, the Japanese Society for Bone and Mineral Research, and the Japan Endocrine Society. J Bone Miner Metab 2015;33:467–73.
59. Hall AM, Bass P, Unwin RJ. Drug-induced renal Fanconi syndrome. QJM 2014;107:261–9.
60. Holick MF. Vitamin D deficiency. N Engl J Med 2007;357:266–81.
61. Hruska KA, Teitelbaum SL. Renal osteodystrophy. N Engl J Med 1995;333:166–74.
62. Kiely PD, Chow J, Eastwood JB, Bourke BE. Fluorosis and osteomalacia. Arthritis Rheum 1999;42:2012–3.
63. Moorthi RN, Moe SM. CKD-mineral and bone disorder: core curriculum 2011. Am J Kidney Dis 2011;58:1022–36.
64. Reginster JY. The high prevalence of inadequate serum vitamin D levels and implications for bone health. Curr Med Res Opin 2005;21:579–86.
65. Whyte MP. Hypophosphatasia: aetiology, nosology, pathogenesis, diagnosis and treatment. Nat Rev Endocrinol 2016;12:233–46.

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Risk of Hospitalized Infection and Initiation of Abatacept Versus Tumor Necrosis Factor Inhibitors Among Patients With Rheumatoid Arthritis: A Propensity Score–Matched Cohort Study

Sarah K. Chen, Katherine P. Liao, Jun Liu, and Seoyoung C. Kim

Objective. We aimed to evaluate the comparative risk of hospitalized infection among patients with rheumatoid arthritis (RA) who initiated abatacept versus a tumor necrosis factor inhibitor (TNFi).

Methods. Using claims data from Truven MarketScan database (2006–2015), we identified patients with RA ages ≥18 years with ≥2 RA diagnoses who initiated treatment with abatacept or a TNFi. The primary outcome was a composite end point of any hospitalized infection. Secondary outcomes included bacterial infection, herpes zoster, and infections affecting different organ systems. We performed 1:1 propensity score (PS) matching between the groups in order to control for baseline confounders. We estimated incidence rates (IRs) and hazard ratios (HRs) with 95% confidence intervals (95% CIs) for hospitalized infection.

Results. We identified 11,248 PS-matched pairs of patients who initiated treatment with abatacept and TNFi with a median age of 56 years (83% were women). The IR per 1,000 person-years for any hospitalized infection was 37 among patients who initiated treatment with abatacept and 47 in those who initiated treatment with TNFi. The HR for the risk of any hospitalized infection associated with abatacept versus TNFi was 0.78 (95% CI 0.64–0.95) and remained lower when compared to infliximab (HR 0.63 [95% CI 0.47–0.85]), while no significant difference was seen when compared to adalimumab and etanercept. The risk of secondary outcomes was lower for abatacept for pulmonary infections, and similar to TNFi for the remaining outcomes.

Conclusion. In this large cohort of patients with RA who initiated treatment with abatacept or TNFi as a first- or second-line biologic agent, we found a lower risk of hospitalized infection after initiating abatacept versus TNFi, which was driven mostly by infliximab.

INTRODUCTION

Rheumatoid arthritis (RA) patients are at increased risk of infection compared to non-RA patients (1–3). Part of this elevated risk is secondary to RA disease and is due to the impaired ability of the immune system to recognize and fight off infections (4,5). While new immunosuppressive therapies have led to dramatic improvements in controlling RA disease activity and damage, the risk of infection is further increased by immunosuppression, especially with the use of biologic disease-modifying antirheumatic drugs (DMARDs) (6,7). Tumor necrosis factor inhibitors (TNFi) and abatacept are both biologic DMARDs, used either as monotherapy or in combination with a nonbiologic DMARD, with comparable efficacy in the treatment of RA (8). However, the 2 therapies may differ in the risk of infection with their use.

Infections are frequent adverse events associated with TNFi therapy in RA and the risk of infection with TNFi use is higher than with nonbiologic DMARD use (6,9,10). While randomized clinical trial data for abatacept did not demonstrate increased risk of serious infections compared to placebo initially, subsequent studies have reported increased incidence of serious infections with its use, with reported IR for infection of 3.1 per 100 patient-years (11–15). Although this rate is lower than the reported IR for TNFi of 6 per 100 patient-years (6), there is a paucity of studies that have compared the 2 therapies directly. To date, no randomized clinical trial has compared the risk of infections between the different

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SIGNIFICANCE & INNOVATIONS

- The comparative safety from infection risk that is associated with biologic immunosuppression with TNF inhibitors (TNFi) versus abatacept in patients with rheumatoid arthritis (RA) is unclear.
- In this propensity score–matched study of 11,248 pairs of patients with RA who initiated treatment with abatacept or TNFi, the incidence rate and risk of hospitalized infections were lower among those who initiated treatment with abatacept (hazard ratio 0.78 [95% confidence interval 0.64–0.95]).
- In subgroup analysis, the risk of infection for abatacept remained lower when compared to those who initiated treatment with infliximab, but not for those who initiated treatment with etanercept and abatacept.
- Use of abatacept is associated with a lower risk of hospitalized infections compared to TNFi among RA patients, particularly when compared to infliximab.

biologic therapies in RA. Previous observational studies have compared the risk of infections between abatacept and TNFi with mixed results (16–19). While some of these studies have demonstrated a lower risk of infection with abatacept, in 1 study the risk was similar between abatacept and TNFi (18).

Given similar efficacy between abatacept and TNFi as biologic therapies for treatment of RA, one of the main determinants in choosing between the medications is minimizing the risk of infection. Therefore, the aim of this study was to compare the risk of hospitalized infections among patients with RA who initiate treatment with abatacept versus treatment with TNFi in the real-world setting using a large US nationwide claims database. We hypothesized that the rates and risk of hospitalized infection would be lower among patients with RA who initiated treatment with abatacept compared to treatment with TNFi.

MATERIALS AND METHODS

Data source and cohort definitions. We used de-identified medical and pharmacy claims data from the Truven MarketScan database (January 1, 2006 to September 30, 2015), which contains longitudinal, comprehensive health care data for most commercially insured individuals in the US from all 50 states (20).

We identified RA patients ages 18 years and older with at least 2 RA International Classification of Diseases, Ninth Revision (ICD-9) codes (714.xx) separated by 7–365 days (21). Among these patients with RA, we selected those who were new to treatment with abatacept or TNFi (adalimumab, certolizumab, etanercept, golimumab, and infliximab) by the National Drug Codes or J codes, with no dispensing of the medication during at least 365 days of continuous enrollment preceding the date of first dispensing (i.e., index date) of abatacept or TNFi. Patients were required to have the second RA diagnosis code on or before the index date. A diagram of the cohort and study design is presented in Supplementary Figure 1, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23824/abstract. For abatacept, we allowed patients to have been treated with nonbiologic DMARDs or TNFi during the baseline period. For those who initiated treatment with TNFi, we allowed patients to have received treatment with nonbiologic DMARDs or abatacept during the baseline period. We excluded patients who were treated with rituximab, tocilizumab, or tofacitinib prior to the index date from the 2 groups, because treatment with other biologic DMARDs could affect the risk of infection during follow-up. We also excluded patients with malignancy, renal dialysis, HIV/AIDS, and history of solid or bone marrow transplantation at baseline, as these are other known comorbidities that would increase the risk of infection.

Study patients were followed from the day following index date, until the earliest event of death, end of enrollment, switching of therapy from abatacept to TNFi or from TNFi to abatacept, or outcome occurrence. In our primary analysis, we censored patients using as-treated analysis, which used a threshold of <30 days of treatment or dispensing gap. In a separate sensitivity analysis, we allowed for any gap in treatment and censored patients at the last drug available date.

Data collection. During the 365-day period prior to the index date, we collected baseline covariates that may be related to infectious risk, including demographics (age, sex, calendar year of index date, region of residence), comorbidities (including hypertension, diabetes mellitus, obesity, smoking, alcohol use, depression, cardiovascular disease, chronic renal disease, chronic liver disease, pulmonary disease, viral hepatitis, inflammatory bowel disease), and hospitalization for infection by ICD-9 codes, and calculated combined comorbidity index at baseline (22). We measured health care utilization characteristics, including number of outpatient physician visits to primary care providers and specialists, emergency department visits, acute care hospitalizations, history of influenza vaccination and pneumonia vaccination, and number of unique generic drug prescriptions at baseline.

We assessed the use of nonbiologic DMARDs, including methotrexate, hydroxychloroquine, leflunomide, sulfasalazine, cyclosporine, tacrolimus, azathioprine, auranofin, and penicillamine. We also measured treatment with glucocorticoids as any recent use in the 30 days prior to the index date, any treatment during the 365 days prior to the index date, and cumulative prednisone-equivalent dose for the 365-day baseline period, calculated based on the total amount in milligrams of prednisone prescribed. We assessed any baseline use of nonsteroidal antiinflammatory drugs, cyclooxygenase 2 enzyme inhibitors, and proton-pump inhibitors. We also assessed the

use of opioids, antibiotics, and zoster treatment during the 365 days of baseline, and recent treatment within 30 days prior to the index date.

Outcomes. The primary outcome was the composite end point of any hospitalized infection including bacterial, viral, or opportunistic infection based on the principal diagnosis for hospitalization. We assessed secondary outcomes of bacterial infection, herpes zoster, and infections by affected organ system (bone/joint, cardiac, gastrointestinal, genitourinary, respiratory, skin/soft tissue, neurologic), based on the principal diagnosis for hospitalization. We used ICD-9 codes to identify hospitalized infection as previously described, with positive predictive value >80% (16,23–25).

Statistical methods. We compared the baseline characteristics of the abatacept and TNFi cohorts. To control for over 40 potential confounders simultaneously, we generated propensity score (PS) for the predicted probability of a patient initiating abatacept versus TNFi given patient characteristics at baseline. We then performed a 1:1 PS nearest neighbor matching using a caliper of 0.025 on the PS scale (26). We compared the covariate balance after matching using standardized differences, and considered the absolute standard mean difference of <0.1 as balanced between the 2 matched groups (27). After PS matching, we estimated the incidence rates (IRs) of the primary and secondary outcomes per 1,000 person-years in the 2 treatment groups. We used Cox proportional hazards models to estimate the hazard ratios (HRs) and 95% confidence intervals (95% CIs) for primary and secondary outcomes. In order to ensure that the proportional hazards assumption was not violated, we included the interaction term of exposure medication and survival time as a time-dependent covariate in our Cox model.

We performed separate PS matching for abatacept versus the 3 most commonly prescribed TNFi (adalimumab, etanercept, and infliximab) and calculated the IR per 1,000 person-years and HR for the primary outcome of any hospitalized infection. In another sensitivity analysis, we identified any PS-matched patients who were treatment naive and had not received either TNFi or abatacept in the baseline period and calculated the IR and HR for primary and secondary outcomes.

All analyses were conducted using SAS, version 9.4. The Institutional Review Board of the Brigham and Women's Hospital approved this study.

RESULTS

We identified 13,015 patients with RA who had newly initiated treatment with abatacept and 52,719 RA patients who had newly initiated treatment with a TNFi (Figure 1). After 1:1 PS matching, there were 11,248 pairs of patients who had initiated treatment with abatacept and TNFi. Baseline covariates were balanced after PS matching with absolute standardized mean difference <0.1. Prior to matching, the abatacept cohort was slightly older (mean ± SD age 54.8 ± 12.8 years versus mean ± SD age 52.1 ± 12.8 years) with a higher proportion of women (83% versus 76%) (Table 1). After PS matching, the abatacept cohort had a mean

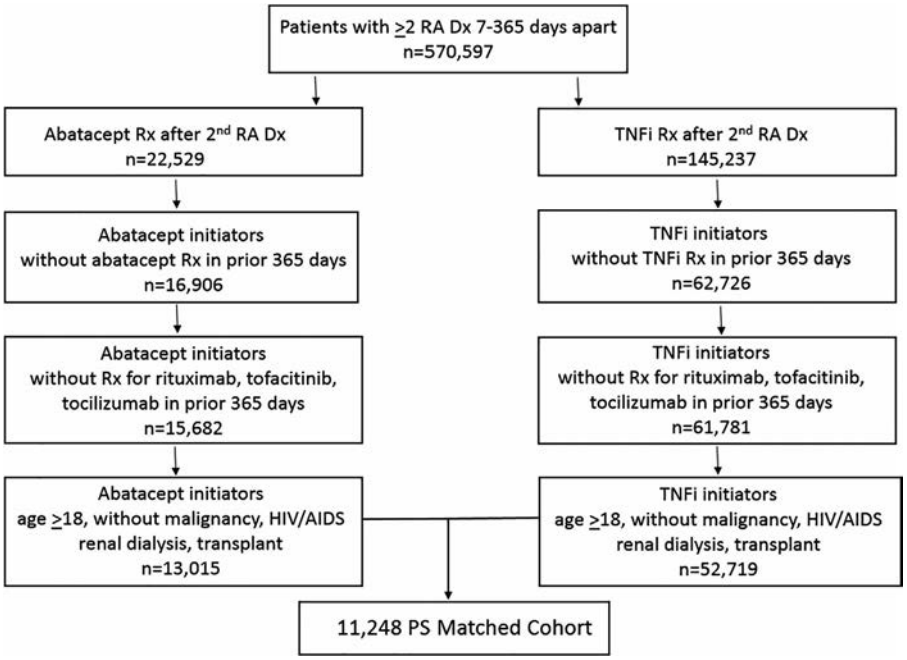

Figure 1. Flow chart of study cohort selection. RA = rheumatoid arthritis; Dx = diagnosis; Rx = prescription; TNFi = tumor necrosis factor inhibitor; PS = propensity score.

Table 1. Baseline characteristics of study cohorts, prior to and after 1:1 propensity score-matching*

	Prior to matching		Propensity score-matched	
	Abatacept n = 13,015	TNFi n = 52,719	Abatacept n = 11,248	TNFi n = 11,248
Demographics				
Age, mean ± SD years	54.8 ± 12.8	52.1 ± 12.8	55.3 ± 12.8	55.5 ± 12.7
Women	83	76	83	84
Region				
Northeast	13	14	13	13
South	39	40	39	39
North central	21	22	21	21
West	15	16	15	15
Unknown	11	9	12	12
Comorbidities				
Obesity	9	9	9	9
Smoking	12	12	12	13
Alcohol use	1	1	1	1
Depression	12	11	12	12
Diabetes	17	15	18	18
Hypertension	42	37	43	43
Hyperlipidemia	32	30	32	32
Cardiovascular disease	56	49	57	57
Heart failure	4	2	4	5
Pulmonary disease	19	16	20	20
Chronic kidney disease	4	3	4	4
Chronic liver disease	5	5	5	5
Viral hepatitis	1	1	1	1
Inflammatory bowel disease	1	3	1	1
Hospitalized infection	3	2	3	3
Combined comorbidity score, mean ± SD	0.54 ± 1.38	0.38 ± 1.18	0.57 ± 1.42	0.58 ± 1.43
Health care utilization				
No. PCP visits, mean ± SD	6.1 ± 7.8	5.3 ± 6.5	6.1 ± 7.9	6.1 ± 7.9
No. rheumatology visits, mean ± SD	4.5 ± 4.7	3.4 ± 3.7	4.4 ± 4.7	4.2 ± 4.7
ED visits	31	28	31	31
Any hospitalization	17	13	18	18
No. unique prescriptions, mean ± SD	14.4 ± 8.2	13.2 ± 7.5	14.1 ± 8.3	14.1 ± 8.2
Flu vaccination	30	25	29	29
Pneumonia vaccination	7	8	7	7

* Values are the percent of patients unless indicated otherwise. TNFi = tumor necrosis factor inhibitor; PCP = primary care physician; ED = emergency department.

age of 55.3 ± 12.8 with 83% women, and the TNFi cohort had a mean ± SD age of 55.5 ± 12.7 years with 84% women.

The prevalence of several comorbidities was slightly higher among the abatacept cohort, including diabetes mellitus, hypertension, cardiovascular disease, and pulmonary disease, but was well balanced between the 2 cohorts after PS matching. The combined comorbidity score was also higher among the abatacept cohort compared to the TNFi cohort (0.54 ± 1.38 versus 0.38 ± 1.18), and after PS matching was similar between the 2 cohorts (0.57 ± 1.42 versus 0.58 ±1.43). Measures of health care utilization were also generally higher in the abatacept cohort but were balanced after PS matching. Baseline hospitalized infection prevalence was 3% for both PS-matched cohorts.

Use of RA-related medication was well-balanced between the PS-matched cohorts, although prior to matching there was a lower prior use of methotrexate, hydroxychloroquine, and sulfasalazine in the abatacept cohort (Table 2). Steroid use was prevalent among both cohorts at 30 days prior to the index date (44% for abatacept, 42% for TNFi), and at 365 days prior (70% versus 69%). Notably, 58% of the abatacept cohort had prescription dispensing for TNFi in the baseline period, compared to 4% of TNFi cohort patients who had prescription dispensing for abatacept.

The overall IR of the primary outcome for the composite end point of any hospitalized infections in our PS-matched cohorts was 36.7 per 1,000 person-years (95% CI 31.8–42.3) for abatacept compared to 47.4 per 1,000 person-years (95% CI 41.5–54.1) for TNFi using as-treated analysis allowing for <30 days gap in treatment (Table 3). In the primary as-treated analysis allowing for <30 days gap in treatment, the mean follow-up time on active treatment was 0.46 ± 0.70 years for the abatacept group, and 0.41 ± 0.66 years for the TNFi group. The risk of hospitalized infection in abatacept was lower compared to TNFi initiators with a HR of 0.78 (95% CI 0.64–0.95).

In our PS-matched sensitivity analyses between abatacept and the 3 most common TNFi, we found that the HR

Table 2. Baseline medications of study cohorts, prior to and after 1:1 PS matching*

	Prior to matching		PS-matched	
	Abatacept†	TNFi‡	Abatacept§	TNFi§
Prior use of biologic DMARDs				
Abatacept	0	2	0	4
TNFi	64	0	58	0
Adalimumab	24	0	16	0
Certolizumab	4	0	2	0
Etanercept	24	0	16	0
Golimumab	4	0	3	0
Infliximab	21	0	20	0
Prior use of nonbiologic DMARDs				
Methotrexate	56	69	55	55
Hydroxychloroquine	23	27	23	23
Leflunomide	18	14	18	18
Sulfasalazine	9	12	9	8
Other#	8	5	8	8
Steroid use	70	69	68	67
Recent steroid use (30 days prior)	44	42	43	43
Steroids cumulative dose 365 days (mg), mean ± SD	1,235.9 (3,484.3)	1,184.7 (9,042.6)	1,192.9 (3,572.8)	1,191.6 (6,178.4)
Other medications				
Antibiotics	69	64	69	68
Recent antibiotics (30 days prior)	19	16	19	19
Antiviral for zoster	8	6	8	8
Recent antiviral for zoster	3	2	3	3
NSAIDs	44	54	43	42
COXIBs	11	11	11	11
Opioids	68	64	67	67
Recent opioids (30 days prior)	40	33	39	40
Proton-pump inhibitors	30	26	30	30

* Values are the percent of patients in the study cohort unless indicated otherwise. PS = propensity score; TNFi = tumor necrosis factor inhibitor; DMARDs = disease-modifying antirheumatic drugs; NSAIDs = nonsteroidal antiinflammatory drugs.
† N = 13,015.
‡ N = 52,719.
§ N = 11,248.
# Other nonbiologic DMARDs included cyclosporine, tacrolimus, azathioprine, auranofin, penicillamine.

remained decreased for abatacept compared to infliximab (HR 0.63 [95% CI 0.47–0.85]), but not statistically significantly higher or lower when compared to adalimumab (HR 0.78 [95% CI 0.57–1.06]) and etanercept (HR 1.19 [95% CI 0.92–1.53]) (Table 4). In a separate sensitivity analysis, using as-treated analysis that allowed for any gap in treatment, the risk of infection was attenuated toward the null. When we broadened our outcome definition of infections using diagnosis codes at any position and not limited to the principal diagnosis code for hospitalization, the results were similar with HR of infection for abatacept compared to TNFi of 0.79 (95% CI 0.68–0.92). In secondary analyses assessing risk of separate types of infections, the HR was lower for respiratory infections among patients who initiated treatment with abatacept compared to TNFi (Table 5). However, there was no significant difference in the risk of the other types of infections between the abatacept and TNFi cohorts.

Because patients who had initiated treatment with abatacept could have been treated with TNFi previously, and those who initiated TNFi could similarly have been previously

Table 3. Risk of hospitalized infection in abatacept versus TNFi initiation: 1:1 PS-matched analysis (n = 11,248)*

	Abatacept		TNFi	
	As-treated (<30 days gap)	As-treated (Any gap)	As-treated (<30 days gap)	As-treated (Any gap)
No. events	188	298	219	321
PYs	5,126	8,201	4,621	7,639
IR (95% CI)†	36.7 (31.8–42.3)	36.3 (32.4–40.7)	47.4 (41.5–54.1)	42.0 (37.7–46.9)
HR (95% CI)†	0.78 (0.64–0.95)	0.86 (0.74–1.01)	1.0	1.0

* TNFi = tumor necrosis factor inhibitor; PS = propensity score; PYs = person-years; IR = incident rate; 95% CI = 95% confidence interval; HR = hazard ratio.
† Per 1,000 PYs.

Table 4. Risk of hospitalized infection in abatacept versus adalimumab, etanercept, and infliximab: 1:1 PS-matched analyses*

	Abatacept			TNFi		
	Abatacept vs. adalimumab	Abatacept vs. etanercept	Abatacept vs. infliximab	Abatacept vs. adalimumab	Abatacept vs. etanercept	Abatacept vs. infliximab
No. patients	3,737	4,550	2,118	3,737	4,550	2,118
No. events	77	128	70	85	112	104
PYs	2,668	3,161	1,677	2,306	3,284	1,573
IR (95% CI)†	28.9 (23.1–36.1)	40.5 (34.1–48.2)	41.8 (33.0–52.8)	36.9 (29.8–45.6)	34.1 (28.3–41.1)	66.1 (54.5–80.1)
HR (95% CI)	0.78 (0.57–1.06)	1.19 (0.92–1.53)	0.63 (0.47–0.85)	1.0 (referent)	1.0 (referent)	1.0 (referent)

* See Table 3 for definitions.
† Per 1,000 PYs.

treated with abatacept, we conducted sensitivity analysis for our primary and secondary outcomes for only patients who were treatment naive to both therapies during the baseline period (see Supplementary Table 1, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23824/abstract). After PS matching, we identified 4,574 treatment-naive patients who initiated abatacept and an equal number of patients who initiated TNFi. The HR for any hospitalized infection for abatacept compared to TNFi was 0.87 (95% CI 0.68–1.11).

DISCUSSION

Patients with RA are at increased risk of infections and this risk is further increased with use of immunosuppressive therapy. Whether there is a difference in infectious risk conferred by different biologic DMARDs is unclear. In this US nationwide study of patients with RA, we found that the IR and risk of hospitalized infections were lower among patients who initiated treatment with abatacept compared to TNFi. This difference in risk appears to be mostly driven by lower infection risk when compared to infliximab. In our secondary outcome analysis, risk of respiratory infections (e.g., pneumonia, empyema, upper respiratory tract infections) was also lower among patients in the abatacept cohort compared to the TNFi cohort. However, there was no significant difference in the risk of hospitalized infections by the remaining types of infections or by affected organ systems.

The IR for infections found in our study are similar to what has been reported for abatacept and TNFi in the literature, with reported IR for abatacept of 31 per 1,000 person-years, and 60 per 1,000 person-years for TNFi in separate studies (6,13). Further, the results are in line with most of the other studies that have compared the risk of infection between abatacept and TNFi. In a previous cohort study using Truven MarketScan data comparing the risk of infections in patients with RA who were switching from first-line TNFi to rituximab, another TNFi, or abatacept, the risk of infection was similar after switching to abatacept versus rituximab (19). However, the infection risk was higher for those switching to another TNFi compared to rituximab. Similarly, a cohort study using Medicare data that included RA patients who were previously treated with a biologic agent and had newly switched to a different TNFi, rituximab, tocilizumab, or abatacept found that the risk of 1-year hospitalized infection was higher in the etanercept (HR 1.24 [95% CI 1.07–1.45]), infliximab (HR 1.39 [95% CI 1.21–1.60]), and rituximab (HR 1.36 [95% CI 1.21–1.53]) groups compared to abatacept as reference (17).

Table 5. Risk of secondary outcomes in 11, 248 patients for abatacept versus TNFi initiation: 1:1 PS-matched analysis for as-treated (<30 days gap)*

	Abatacept				TNFi			
	No. events	PYs	IR (95% CI)	HR (95% CI)	No. events	PYs	IR (95% CI)†	HR (95% CI)
Bacterial infection	100	5,160	19.4 (15.9–23.6)	0.81 (0.62–1.06)	112	4,621	24.0 (20.0–28.9)	1.0
Herpes zoster	81	5,141	15.8 (12.7–19.6)	1.00 (0.73–1.37)	73	4,639	15.7 (12.5–19.8)	1.0
By organ system								
Bone/joint	7	5,190	1.4 (0.6–2.8)	0.91 (0.32–2.60)	7	4,696	1.5 (0.7–3.1)	1.0
Cardiac	0	5,191	–	–	1	4,697	0.2 (<0.1–1.5)	1.0
Gastrointestinal	20	5,186	3.9 (2.5–6.0)	0.75 (0.41–1.35)	24	4,689	5.1 (3.4–7.6)	1.0
Genitourinary	17	5,185	3.3 (2.0–5.3)	1.04 (0.52–2.07)	15	4,690	3.2 (1.9–5.3)	1.0
Respiratory	65	5,160	12.6 (9.9–16.1)	0.71 (0.52–0.99)	83	4,666	17.8 (14.4–22.1)	1.0
Skin/soft tissue	30	5,179	5.8 (4.1–8.3)	0.68 (0.42–1.09)	40	4,683	8.5 (6.3–11.6)	1.0
Neurologic	1	5,191	0.2 (<0.1–1.4)	0.91 (0.06–14.5)	1	4,697	0.2 (<0.1–1.5)	1.0

* See Table 3 for definitions.
† Per 1,000 PYs.

In another previous study that used administrative claims data from 2005 to 2009, among RA patients who were initiating or switching biologic DMARD therapy, those who were treated with abatacept had lower rates of hospitalized infection compared to infliximab (HR 0.68 [95% CI 0.48–0.96]) (16). The risk of infection was also lower for treatment with adalimumab and etanercept compared to infliximab in that study, while in our study we observed a lower infection risk for abatacept compared to infliximab (HR 0.63 [95% CI 0.47–0.85]), a numerically lower risk for abatacept compared to adalimumab (HR 0.78 [95% CI 0.57–1.06]), and similar risk for abatacept compared to etanercept (Table 4).

In a predominantly male RA cohort of US veterans from 1998 to 2011, the risk of hospitalized bacterial infections was similar between in patients treated with abatacept compared to those treated with etanercept (HR 1.1 [95% CI 0.6–21]), with an IR for abatacept of 28 per 1,000 person-years (95% CI 17–47) (18). These rates are in line with the findings in our study, with an HR of 0.81 (95% CI 0.62–1.06) for risk of hospitalized bacterial infections between patients treated with abatacept compared to those treated with etanercept and an IR for abatacept of 19.4 per 1,000 person-years (95% CI 15.9–23.6). Additionally, similar to the results of our study, previous studies that have compared the risk of herpes zoster infections found no difference in the risk of zoster infections between treatment with abatacept and TNFi, with the IR of zoster infections slightly higher for abatacept in previously reported literature (IR 23.3 per 1,000 person-years [95% CI 20.4–26.7] in 1 study [28] and IR 18.7 per 1,000 person-years [95% CI 15.8–22.0] in another [29]) compared to our study IR of 15.7 per 1,000 person-years (95% CI 12.7–19.6) in abatacept and 15.7 per 1,000 person-years (95% CI 12.5–19.8) in TNFi.

In our separate analysis comparing the risk of hospitalized infection in patients who initiated treatment with abatacept versus the 3 most commonly prescribed TNFi, we found that the lower risk of hospitalized infection in those who initiated abatacept compared to TNFi was driven mostly by infliximab initiation (HR 0.63 [95% CI 0.47–0.85]). The risk remained numerically, not statistically, significant, lower for abatacept in comparison to adalimumab initiation (HR 0.78 [95% 0.57–1.06]), but the infection risk associated with abatacept was noted to be not significantly higher versus etanercept (HR 1.19 [95% CI 0.92–1.53]). These results are in line with previous findings of lower risk of serious infections in patients treated with etanercept compared to infliximab and adalimumab in a prospective cohort of RA patients in a Dutch registry (30). There are several potential explanations for this observed difference among TNFi. The peak concentration of infliximab (delivered as an intravenous infusion) is higher than that of adalimumab and etanercept, which are administered as subcutaneous injections (31). Additionally, the clearance of etanercept is significantly higher with lower steady-state drug level compared to infliximab and adalimumab, and the binding avidity to TNF subunits is lower for etanercept (1:1 ratio), compared to infliximab (up to 3:1 ratio) (31,32). Furthermore, etanercept is a TNF receptor fusion protein that binds only circulating TNF, while infliximab is a monoclonal antibody against TNF and additionally has a cytotoxic effect by binding to cells that express TNF on their membranes (33).

Our study has several strengths as a large cohort of US patients with RA in a nationwide database with a new user design with active comparator. In comparison to the previously mentioned studies, we used PS matching to minimize confounding by indication and control for imbalance among the abatacept and TNFi treatment groups (including patient characteristics and regional variation) and adjusted for a large number of baseline confounders between the 2 cohorts (such as prior antibiotic and antiviral use and history of vaccinations). We directly compared the IR and risk of infection between abatacept and TNFi and found lower IR of infections for abatacept compared to TNFi, similar to the reported IR in the literature, and lower risk of infection among patients who initiated treatment with abatacept. The reason for this decreased risk of infection that was found in our study and previous studies is unknown but may potentially be due to the fact that abatacept indirectly blocks T cell costimulation rather than the mechanism of direct inhibition of cytokines for TNFi (11).

In a separate as-treated analysis, allowing for any gap in treatment, there was no significant difference in risk of infection between the abatacept and TNFi cohorts. In our primary analysis, we used an as-treated analysis with <30 days of gap in treatment, which requires high treatment adherence. Using this design, we observed a lower risk of hospitalized infection in those who initiated treatment with abatacept. This suggests that there may be selection bias for patients who are more adherent or continued on therapy versus those who discontinue therapy for those taking abatacept versus TNFi. Although it is not possible to ascertain the reasons for stopping the therapy after initiation using claims databases, one possibility is that there is a lower threshold to stop or switch from TNFi therapy if there was concern of risk of infection such as minor infections, which may lower the rates of hospitalized infections for TNFi compared to abatacept.

It is notable that in our study, which examined first-line or subsequent-line initiation of abatacept or TNFi, 58% of the abatacept cohort was previously taking TNFi in the baseline period and would be classified as switchers, compared to only 4% of TNFi cohort who had previously used abatacept. In our sensitivity analysis, among patients who were treatment naive to both abatacept and TNFi, the lower risk of infection among those who initiated treatment with abatacept compared to TNFi was attenuated toward the null. This suggests a potential role of RA disease severity of treatment history in addition to the types of biologics on the risk of infection in patients with RA.

Our study has limitations. Although we used PS matching for confounding control, there is still a concern for partially measured covariates and lack of information on other covariates that may affect risk of infection. For instance, RA disease activity is an important factor that can affect the risk of infections (34),

but is a covariate we are unable to capture in a claims database (35–38). Therefore, we included measures of steroid use, nonbiologic DMARD use, number of rheumatology visits, and combined comorbidity index as covariates in our PS matching. Steroid use, which was a covariate in our analysis, is another important factor in risk of infections and may be indirectly related to disease activity. However, there may be discrepancies between the steroid dispensing measured in our study and actual use by patients (39–41). We also attempted to assess serostatus as a covariate but were limited by power because <3% of patients in each cohort had available laboratory results. Additionally, socioeconomic status and race/ethnicity are important demographic factors in the US that contribute to health disparities and outcomes that we were unable to collect and adjust for in our study (42,43).

In this large nationwide cohort of patients with RA in the US who initiated abatacept or a TNFi as a first- or second-line biologic therapy, we found a lower risk of any hospitalized infections associated with abatacept versus TNFi, particularly in comparison to infliximab, suggesting that RA patients with specific concerns about infections may benefit from the use of abatacept compared to TNFi.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publications. Drs. Chen and Kim had full access to all of the data in the study and take responsibility for the integrity for the data and the accuracy of the data analysis.

Study conception and design. Chen, Liao, Liu, Kim.
Acquisition of data. Chen, Liu, Kim.
Analysis and interpretation of data. Chen, Liao, Liu, Kim.

REFERENCES

1. Doran MF, Crowson CS, Pond GR, O'Fallon WM, Gabriel SE. Frequency of infection in patients with rheumatoid arthritis compared with controls: a population-based study. Arthritis Rheum 2002;46:2287–93.
2. Mitchell DM, Spitz PW, Young DY, Bloch DA, McShane DJ, Fries JF. Survival, prognosis, and causes of death in rheumatoid arthritis. Arthritis Rheum 1986;29:706–14.
3. Smitten AL, Choi HK, Hochberg MC, Suissa S, Simon TA, Testa MA, et al. The risk of hospitalized infection in patients with rheumatoid arthritis. J Rheumatol 2008;35:387–93.
4. Mikuls TR. Co-morbidity in rheumatoid arthritis. Best Pract Res Clin Rheumatol 2003;17:729–52.
5. Wagner UG, Koetz K, Weyand CM, Goronzy JJ. Perturbation of the T cell repertoire in rheumatoid arthritis. Proc Natl Acad Sci U S A 1998;95:14447–52.
6. Listing J, Strangfeld A, Kary S, Rau R, von Hinueber U, Stoyanova-Scholz M, et al. Infections in patients with rheumatoid arthritis treated with biologic agents. Arthritis Rheum 2005;52:3403–12.
7. Ruderman EM. Overview of safety of non-biologic and biologic DMARDs. Rheumatology (Oxford) 2012;51 Suppl 6:vi37–43.
8. Curtis JR, Singh JA. Use of biologics in rheumatoid arthritis: current and emerging paradigms of care. Clin Ther 2011;33:679–707.
9. Strangfeld A, Listing J, Herzer P, Liebhaber A, Rockwitz K, Richter C, et al. Risk of herpes zoster in patients with rheumatoid arthritis treated with anti-TNF-α agents. JAMA 2009;301:737–44.
10. Kroesen S, Widmer AF, Tyndall A, Hasler P. Serious bacterial infections in patients with rheumatoid arthritis under anti-TNF-α therapy. Rheumatology (Oxford) 2003;42:617–21.
11. Genovese MC, Becker JC, Schiff M, Luggen M, Sherrer Y, Kremer J, et al. Abatacept for rheumatoid arthritis refractory to tumor necrosis factor α inhibition. N Engl J Med 2005;353:1114–23.
12. Salliot C, Dougados M, Gossec L. Risk of serious infections during rituximab, abatacept and anakinra treatments for rheumatoid arthritis: meta-analyses of randomised placebo-controlled trials. Ann Rheum Dis 2009;68:25–32.
13. Simon TA, Askling J, Lacaille D, Franklin J, Wolfe F, Covucci A, et al. Infections requiring hospitalization in the abatacept clinical development program: an epidemiological assessment. Arthritis Res Ther 2010;12:R67.
14. Weinblatt M, Combe B, Covucci A, Aranda R, Becker JC, Keystone E. Safety of the selective costimulation modulator abatacept in rheumatoid arthritis patients receiving background biologic and nonbiologic disease-modifying antirheumatic drugs: a one-year randomized, placebo-controlled study. Arthritis Rheum 2006;54:2807–16.
15. Kremer JM, Genant HK, Moreland LW, Russell AS, Emery P, Abud-Mendoza C, et al. Effects of abatacept in patients with methotrexate-resistant active rheumatoid arthritis: a randomized trial. Ann Intern Med 2006;144:865–76.
16. Curtis JR, Xie F, Chen L, Baddley JW, Beukelman T, Saag KG, et al. The comparative risk of serious infections among rheumatoid arthritis patients starting or switching biological agents. Ann Rheum Dis 2011;70:1401–6.
17. Yun H, Xie F, Delzell E, Levitan EB, Chen L, Lewis JD, et al. Comparative risk of hospitalized infection associated with biologic agents in rheumatoid arthritis patients enrolled in Medicare. Arthritis Rheumatol 2016;68:56–66.
18. Curtis JR, Yang S, Patkar NM, Chen L, Singh JA, Cannon GW, et al. Risk of hospitalized bacterial infections associated with biologic treatment among US veterans with rheumatoid arthritis. Arthritis Care Res (Hoboken) 2014;66:990–7.
19. Johnston SS, Turpcu A, Shi N, Fowler R, Chu BC, Alexander K. Risk of infections in rheumatoid arthritis patients switching from anti-TNF agents to rituximab, abatacept, or another anti-TNF agent, a retrospective administrative claims analysis. Semin Arthritis Rheum 2013;43:39–47.
20. Desai RJ, Rao JK, Hansen RA, Fang G, Maciejewski M, Farley J. Tumor necrosis factor- inhibitor treatment and the risk of incident cardiovascular events in patients with early rheumatoid arthritis: a nested case-control study. J Rheumatol 2014;41:2129–36.
21. Kim S, Servi A, Polinski J. Validation of rheumatoid arthritis diagnoses in health care utilization data. Arthritis Res Ther 2011;13:R32.
22. Gagne JJ, Glynn RJ, Avorn J, Levin R, Schneeweiss S. A combined comorbidity score predicted mortality in elderly patients better than existing scores. J Clin Epidemiol 2011;64:749–59.
23. Curtis JR, Xie F, Yun H, Saag KG, Chen L, Delzell E. Risk of hospitalized infection among rheumatoid arthritis patients concurrently treated with a biologic agent and denosumab. Arthritis Rheumatol 2015;67:1456–64.
24. Schneeweiss S, Robicsek A, Scranton R, Zuckerman D, Solomon DH. Veteran's affairs hospital discharge databases coded serious bacterial infections accurately. J Clin Epidemiol 2007;60:397–409.
25. Patkar NM, Curtis JR, Teng GG, Allison JJ, Saag M, Martin C, et al. Administrative codes combined with medical records based criteria accurately identified bacterial infections among rheumatoid arthritis patients. J Clin Epidemiol 2009;62:321–7.e7.

26. Ripollone JE, Huybrechts KF, Rothman KJ, Ferguson RE, Franklin JM. Implications of the propensity score matching paradox in pharmacoepidemiology. Am J Epidemiol 2018;187:1951–61.
27. Austin PC. Using the Standardized difference to compare the prevalence of a binary variable between two groups in observational research. Commun Stat Simul Comput 2009;38:1228–34.
28. Curtis JR, Xie F, Yun H, Bernatsky S, Winthrop KL. Real-world comparative risks of herpes virus infections in tofacitinib and biologic-treated patients with rheumatoid arthritis. Ann Rheum Dis 2016;75:1843–7.
29. Yun H, Xie F, Delzell E, Chen L, Levitan EB, Lewis JD, et al. Risks of herpes zoster in patients with rheumatoid arthritis according to biologic disease-modifying therapy. Arthritis Care Res (Hoboken) 2015;67:731–6.
30. Van Dartel SA, Fransen J, Kievit W, Flendrie M, den Broeder AA, Visser H, et al. Difference in the risk of serious infections in patients with rheumatoid arthritis treated with adalimumab, infliximab and etanercept: results from the Dutch Rheumatoid Arthritis Monitoring (DREAM) registry. Ann Rheum Dis 2013;72:895–900.
31. Furst DE, Wallis R, Broder M, Beenhouwer DO. Tumor necrosis factor antagonists: different kinetics and/or mechanisms of action may explain differences in the risk for developing granulomatous infection. Semin Arthritis Rheum 2006;36:159–67.
32. Scallon B, Cai A, Solowski N, Rosenberg A, Song XY, Shealy D, et al. Binding and functional comparisons of two types of tumor necrosis factor antagonists. J Pharmacol Exp Ther 2002;301:418–26.
33. Scallon BJ, Moore MA, Trinh H, Knight DM, Ghrayeb J. Chimeric anti-TNF-α monoclonal antibody cA2 binds recombinant transmembrane TNF-α and activates immune effector functions. Cytokine 1995;7:251–9.
34. Au K, Reed G, Curtis JR, Kremer JM, Greenberg JD, Strand V, et al. High disease activity is associated with an increased risk of infection in patients with rheumatoid arthritis. Ann Rheum Dis 2011;70:785–91.
35. Wolfe F, Michaud K, Simon T. Can severity be predicted by treatment variables in rheumatoid arthritis administrative data bases? J Rheumatol 2006;33:1952–6.
36. Ting G, Schneeweiss S, Scranton R, Katz JN, Weinblatt ME, Young M, et al. Development of a health care utilisation data-based index for rheumatoid arthritis severity: a preliminary study. Arthritis Res Ther 2008;10:R95.
37. Desai RJ, Solomon DH, Weinblatt ME, Shadick N, Kim SC. An external validation study reporting poor correlation between the claims-based index for rheumatoid arthritis severity and the disease activity score. Arthritis Res Ther 2015;17:83.
38. Vinet E, Kuriya B, Widdifield J, Bernatsky S. Rheumatoid arthritis disease severity indices in administrative databases: a systematic review. J Rheumatol 2011;38:2318–25.
39. Saag KG, Koehnke R, Caldwell JR, Brasington R, Burmeister LF, Zimmerman B, et al. Low dose long-term corticosteroid therapy in rheumatoid arthritis: an analysis of serious adverse events. Am J Med 1994;96:115–23.
40. Doran MF, Crowson CS, Pond GR, O'Fallon WM, Gabriel SE. Predictors of infection in rheumatoid arthritis. Arthritis Rheum 2002;46:2294–300.
41. Schneeweiss S, Setoguchi S, Weinblatt ME, Katz JN, Avorn J, Sax PE, et al. Anti–tumor necrosis factor α therapy and the risk of serious bacterial infections in elderly patients with rheumatoid arthritis. Arthritis Rheum 2007;56:1754–64.
42. Kawachi I, Daniels N, Robinson DE. Health disparities by race and class: why both matter. Health Aff (Millwood) 2005;24:343–52.
43. Betancourt JR, Green AR, Carrillo JE, Ananeh-Firempong O. Defining cultural competence: a practical framework for addressing racial/ethnic disparities in health and health care. Public Health Rep 2003;118:293–302.

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Longitudinal Occurrence and Predictors of Patient-Provider Discordance Between Global Assessments of Disease Activity in Rheumatoid Arthritis: A Case–Control Study

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Objective. To identify longitudinal predictors of discordance between patients with rheumatoid arthritis (RA) and their health care providers, where patient global assessment of disease activity is substantially higher than provider global assessment.

Methods. This retrospective case–control study included 102 cases with positive discordance (i.e., ≥25 mm between patient and provider global assessments) and 102 controls without discordance who were matched for age, sex, RA duration, and Clinical Disease Activity Index (CDAI) score. Data were collected at the baseline visit (date of diagnosis or earliest available visit), the index visit (participation in a previous cross-sectional study), and at up to 11 additional visits before the index visit. Data included patient characteristics, disease activity measures, Disease Activity Score in 28 joints (3-variable) using the C-reactive protein level (DAS28-CRP), and medications. Data were analyzed by using linear and logistic regression models with smoothing splines for nonlinear trends.

Results. Overall, the mean age was 63 years, 75% of patients were female, and the mean RA duration was 10 years. Compared with controls, cases had higher rates of discordant visits during the 4 years before the index visit, and they had a higher CDAI score and DAS28-CRP earlier in the disease course. Cases more frequently had antinuclear antibodies, nonerosive disease, prior depression, or prior use of antidepressants or fibromyalgia medications. Disease-modifying medication use was not different between cases and controls.

Conclusion. The findings inform new hypotheses about the relationships of disease activity and antinuclear antibodies to the later occurrence of positive discordance among patients with RA.

INTRODUCTION

Discrepancy in assessments of health status is quite common between patients with rheumatic diseases and their health care providers (1). Among patients with rheumatoid arthritis (RA), discordance between patients and their providers in the global assessment of disease activity, in which the patient's global assessment is substantially higher (i.e., ≥25 points on a scale from 0 to 100) than the provider's global assessment, is present in approximately 30% of clinical encounters (2–5). Although management of RA has changed dramatically over the past decades, patient-provider discordance is clearly prevalent. The treat-to-target and tight control strategies have become important in the management of RA (6,7). However, current treatment guidelines do not provide specific guidance for addressing patient-provider discordance in relation to diagnosis, treatment, or medical decision-making. Limited evidence to date suggests that positive discordance is predictive of adverse health-related quality of life, loss of work productivity, and activity impairment at 36 weeks of follow-up (8) and at 2 years of follow-up (9). Addressing these issues in a comprehensive manner should be a major goal of providers for improving patient outcomes and health-related quality of life (8,9).

Little is known about the occurrence of patient-provider discordance. Although many cross-sectional studies have shown the

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No potential conflicts of interest relevant to this article were reported.

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SIGNIFICANCE & INNOVATIONS

- This study is, to the best of our knowledge, among the first to evaluate longitudinal data recorded before positive discordance is identified between patients with rheumatoid arthritis (RA) and their health care providers in global assessments of disease activity, to identify patient-level predictors and to determine the impact of discordance on treatment decisions.
- The main finding is that patients affected by patient-provider discordance may have higher disease activity earlier in the disease course, according to the Clinical Disease Activity Index score and the Disease Activity Score in 28 joints (3-variable) using the C-reactive protein level compared with patients with concordant patient-provider global assessments.
- Other new predictors included positive antinuclear antibodies, nonerosive disease, a history of depression, and previous use of antidepressant or fibromyalgia medications.
- Future research should explore new hypotheses about the relationships of uncontrolled clinical disease activity and the presence of antinuclear antibodies to the eventual occurrence of positive discordance among patients with RA.

prevalence of discordance among patients with RA (2,3,10–13), few studies have investigated how frequently discordance occurs during the disease course and whether discordance persists or resolves after it has occurred (8,9,14). Previous studies have identified numerous potential causes, especially pain due to inflammatory and noninflammatory processes, fatigue, functional disability, depression, psychological distress, low health literacy, and problems with patient-provider communication (2,3,8,10). However, few longitudinal studies have identified predictors of future patient-provider discordance (8,9,14). Knowledge of the predictors of discordance is critical to the design and development of strategies for identification and management to lessen or prevent the occurrence of discordance. Hence, the objectives of our study were to determine the persistence of discordance over time, to identify predictors of future discordance, and to evaluate the impact of discordance on RA treatment decisions.

PATIENTS AND METHODS

Study design and patient population. This was a retrospective case–control study of 204 patients classified as having RA, identified from our previous cross-sectional study (13) of 350 consecutive patients with a clinical diagnosis of RA or inflammatory arthritis who were evaluated at Mayo Clinic in Rochester, Minnesota, between September 2014 and May 2015 (Figure 1). All the study patients fulfilled the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria for RA (15), were ages ≥18 years, and resided within 250 km of Mayo Clinic in Rochester, Minnesota. The index visit was defined as the visit from our previous cross-sectional study on discordance. Cases were defined as having positive discordance (i.e., patient global assessment of disease activity ≥25 mm more than the rheumatology care provider global assessment) at the index visit, and controls were defined as having concordance (i.e, the difference between the patient and provider global assessments was <25 mm) at the index visit. For each of the 102 cases, 1 control was matched for age (± 5 years; median 1.6 years between matched pairs), sex, RA duration (±10 years; median 2.2 years between matched pairs), and Clinical Disease Activity Index (CDAI) score (<10 versus ≥10) (5). In our practice, patients generally return to see the same provider for follow-up visits. The Mayo Clinic Institutional Review Board approved the study and granted a waiver for informed consent. Before abstracting records, we verified that no participants denied use of their medical records for research, according to Minnesota law.

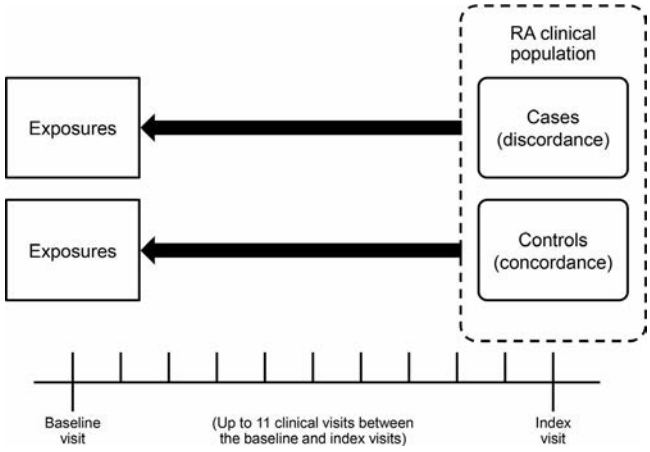

Figure 1. Design of the case–control study. Cases with discordance and controls with concordance between patient and provider global assessments of disease activity were identified at the index visit and matched for age, sex, rheumatoid arthritis (RA) duration, and Clinical Disease Activity Index score. Exposure data were collected at baseline (i.e., the date of diagnosis or earliest available visit when patient and provider global assessments were available) and at up to 11 clinical visits between the baseline and index visits.

Data collection. Data were collected from the electronic health records at the baseline visit (defined as the date of diagnosis or earliest available visit when both patient and provider global assessments were available), the index visit, and up to 11 additional clinical visits before the index visit over the previous 3 to 4 years (Figure 1). At the baseline visit, study variables included duration of symptoms, date of diagnosis, radiographic evidence of erosions, first conventional synthetic or biologic disease-modifying antirheumatic drug (DMARD) used, results of testing for

rheumatoid factor, anti–cyclic citrullinated peptide antibodies, or antinuclear antibodies (ANAs), and use of prednisone, opioids, or antidepressants. Use of methotrexate in the first 6 months after diagnosis was also determined.

Data from each clinical visit included the patient and provider global assessments with the visual analog scale (VAS; range 0–100 mm), pain VAS (range 0–100 mm), tender and swollen joint counts (range 0–28), Health Assessment Questionnaire II (HAQ-II) score (16), CDAI score (17), Disease Activity Score in 28 joints (3-variable) using the C-reactive protein level (DAS28-CRP) (18,19), radiographic evidence of erosions, erythrocyte sedimentation rate (ESR), and the CRP level. Differences between patient and provider global assessments were calculated for each visit, and a discordant visit was defined as any visit with a difference of ≥25 mm. Recorded data also included information on the initiation or modification of treatment with conventional synthetic or biologic DMARDs or glucocorticoids and with opioids, fibromyalgia medications (e.g., duloxetine, pregabalin, and milnacipran), antidepressants, or anxiolytics. For each visit, the presence of comorbidities was also abstracted; these included depression, anxiety, fibromyalgia, and osteoarthritis, and were defined by any history of physician diagnosis.

Statistical analysis. Descriptive statistics (e.g., mean and percentage) were used to summarize the data for cases and controls. Comparisons between groups were performed with the chi-square and Wilcoxon's rank sum tests, and conditional logistic regression models were adjusted for time from the baseline visit to the study visit. Trends over time in characteristics of interest were examined by using generalized linear models with random effects to account for multiple visits per patient. Interactions were examined between case and control status and rates of change in patient characteristics. Smoothing splines were used to examine potential nonlinear trends and to plot the trends over time. Analyses were performed with SAS software, version 9.4, and R software, version 3.1.1.

RESULTS

Patient characteristics at the index discordant visit. The study cohort included 102 cases and 102 controls (Table 1). The majority of patients in both groups were non-Hispanic white, and 75% were female. At the index visit, the mean age was 63 years, the mean RA duration was 10 years, the mean CDAI score was 12 for both cases and controls (P = 0.15), and the mean

Table 1. Patient characteristics at baseline and index visit for cases with patient-provider discordance and control*

Characteristic	Baseline visit			Index visit		
	Controls	Cases	*P*	Controls	Cases	*P*
Patient global assessment (range 0–100), mm	25 ± 22.7	42 ± 24.0	<0.001	31 ± 24.3	59 ± 16.0	<0.001
Provider global assessment (range 0–100), mm	29 ± 28.3	24 ± 19.4	0.94	29 ± 23.7	16 ± 11.6	<0.001
CDAI score	11 ± 10.8	15 ± 10.6	0.001	12 ± 11.5	12 ± 7.9	0.15
CDAI category, no. (%)	–	–	0.02	–	–	0.58
Remission or low disease activity (≤10)	48 (59)	25 (39)	–	55 (54)	51 (50)	–
Moderate or high disease activity (>10)	33 (41)	39 (61)	–	47 (46)	51 (50)	–
Unknown, no.	21	38	–	0	0	–
DAS28-CRP	2.8 ± 1.2	3.5 ± 1.3	0.001	2.9 ± 1.0	3.0 ± 1.2	0.99
DAS28-CRP category	–	–	0.002	–	–	0.54
Remission or low disease activity (≤3.2), no. (%)	43 (70)	21 (41)	–	52 (67)	54 (62)	–
Moderate or high disease activity (>3.2), no. (%)	18 (30)	30 (59)	–	26 (33)	33 (38)	–
Unknown, no.	41	51	–	24	15	–
Pain VAS (0–100), mm	31 ± 26.7	45 ± 23.9	<0.001	35 ± 26.7	58 ± 20.9	<0.001
HAQ-II score	0.6 ± 0.7	0.9 ± 0.7	0.001	0.7 ± 0.6	1.0 ± 0.6	<0.001
Tender joint count (0–28)	3.4 ± 6.4	5.2 ± 6.2	0.002	3.4 ± 5.7	3.0 ± 5.0	0.67
Swollen joint count (0–28)	2.6 ± 4.8	3.1 ± 3.4	0.02	2.8 ± 4.3	2.8 ± 10.1	0.22
ESR, mm/hour	12.6 ± 11.9	17.1 ± 16.8	0.08	12.7 ± 11.9	15.8 ± 16.0	0.41
CRP, mg/liter	5.8 ± 5.4	9.6 ± 14.0	0.13	8.2 ± 14.9	7.4 ± 7.6	0.49
Education level						0.99
Not a high school graduate, no. (%)	–	–	–	5 (5)	5 (5)	–
High school graduate, no. (%)	–	–	–	26 (27)	29 (31)	–
Beyond high school graduate, no. (%)	–	–	–	65 (68)	60 (64)	–
Unknown, no.	–	–	–	6	8	–

* Values are the mean ± SD unless indicated otherwise. For both cases and controls, n = 102. CDAI = Clinical Disease Activity Index; DAS28-CRP = Disease Activity Score in 28 joints (3-variable) using the C-reactive protein level; VAS = visual analog scale; HAQ-II = Health Assessment Questionnaire II; ESR = erythrocyte sedimentation rate.

Table 2. Predictors of patient-provider discordance*

Characteristic	Control (n = 102)	Case (n = 102)	OR (95% CI)†
At baseline visit			
ANA, positive	13/80 (16)	25/80 (31)	3.42 (1.21–9.63)
Discordance (patient global minus provider global), mean ± SD mm	−4 ± 28	22 ± 23	1.74 (1.30–2.32)‡
CDAI score per 12-unit change, mean ± SD	10.8 ± 10.8	15.4 ± 10.6	1.72 (1.04–2.85)
Time from baseline to study visit, mean ± SD years	2.6 ± 1.2	2.6 ± 1.2	0.86 (0.61–1.20)
RF or anti-CCP antibodies, positive	79/100 (79)	70/100 (70)	0.68 (0.35–1.31)
At diagnosis of RA			
Use of methotrexate in first 6 months	63/101 (62)	73/100 (73)	1.67 (0.88–3.16)
Radiographic evidence of erosions, no. (%)	16 (16)	16 (16)	1.09 (0.49–2.38)
Prednisone use, no. (%)	65 (64)	71 (71)	1.32 (0.72–2.39)
At or before the index discordant visit			
Antidepressant use, no. (%)	7 (7)	20 (20)	2.87 (1.21–6.80)
Fibromyalgia medication use, no. (%)	7 (7)	18 (18)	3.20 (1.17–8.74)
Fibromyalgia, no. (%)	10 (10)	18 (18)	2.14 (0.74–5.26)
Depression, no. (%)	27 (26)	40 (39)	1.94 (1.02–3.71)
Osteoarthritis, no. (%)	54 (53)	63 (62)	1.55 (0.83–2.90)
Opioid use, no. (%)	26 (25)	39 (38)	1.77 (0.94–3.22)
NSAID use, no. (%)	71 (70)	74 (73)	1.14 (0.63–2.06)
DMARD/biologic modification, no. (%)	76 (75)	79 (77)	1.16 (0.62–2.18)
Anxiety, no. (%)	19 (19)	13 (13)	0.67 (0.32–1.38)
Radiographic evidence of erosions	56/101 (55)	39/99 (39)	0.43 (0.22–0.83)

* Values are the number of participants/number of participants with available data if less than 102 (%), unless indicated otherwise. OR = odds ratio; 95% CI = 95% confidence interval; ANA = antinuclear antibody; CDAI = Clinical Disease Activity Index; RF = rheumatoid factor; CCP = cyclic citrullinated peptide; RA = rheumatoid arthritis; NSAID = nonsteroidal antiinflammatory drug; DMARD = disease-modifying antirheumatic drug.
† ORs from conditional logistic regression models adjusted for time from baseline to study visit.
‡ OR reported per 10-unit increase.

DAS28-CRP was 3.0 for cases and 2.9 for controls ($P = 0.99$). The mean ± SD patient global assessment was 59 ± 16.0 for cases and 31 ± 24.3 for controls ($P < 0.001$).

Associations of discordance with baseline disease characteristics. The mean ± SD number of visits was similar between cases (6.3 ± 2.9) and controls (5.9 ± 2.7) ($P = 0.33$). For both groups, the mean ± SD time between baseline and index visits was 2.6 ± 1.2 years (median 3.0 years; maximum 4.0 years).

At baseline, the mean ± SD patient global assessment was 42 ± 24.0 mm for cases and 25 ± 22.7 mm for controls ($P < 0.001$). The mean ± SD CDAI score was 15 ± 10.6 for cases and 11 ± 10.8 for controls ($P = 0.001$); similarly, the mean ± SD DAS28-CRP was 3.5 ± 1.3 for cases and 2.8 ± 1.2 for controls ($P < 0.001$) (Table 1). According to both the CDAI score and the DAS28-CRP at baseline, a higher proportion of cases had moderate or high disease activity, whereas a higher proportion of controls was in the remission or low disease activity category; the proportion of patients in the remission or low disease activity category was similar between the cases and controls at the index visit.

At RA diagnosis, no significant differences were observed between cases and controls in the prevalence of comorbid osteoarthritis (32% versus 25%) or fibromyalgia (2% versus 4%). Pain levels were higher for cases compared with controls at baseline. At the index visit, 53% of controls and 62% of cases had a clinical diagnosis of osteoarthritis, and 10% of controls and 18% of cases had a clinical diagnosis of fibromyalgia (Table 2).

Trends in patient-provider discordance over time. Analysis of the trends before the index discordant visit showed that the patient global assessment increased annually by an average of 2.4 mm among controls and 3.7 mm among cases; these values equate to 3-year changes of 7 mm among controls and 11 mm among cases (interaction $P = 0.26$), while the provider global assessment did not change for controls (average change 0.3 mm over 3 years) and decreased by 11 mm over 3 years on average for cases (interaction $P = 0.008$) (Figure 2). Examination of the differences between the patient and provider global assessments over time showed that the patient global assessment was 20 mm more, on average, than the provider global assessment before the study visit, and this discordance increased over 3 years by 21 mm, on average, among the cases and by only 6 mm among controls (interaction $P = 0.001$). Analysis of trends for individual patient-provider dyads revealed evidence of variability, with some patients and providers alternating between discordance and concordance over time (data not shown). However, a greater percentage (70.7% versus 30.0%; $P < 0.001$) and higher rate of discordant visits (1.6 versus 0.6; $P < 0.001$) was observed for cases compared with controls, providing evidence of a tendency of positive discordance to recur or persist.

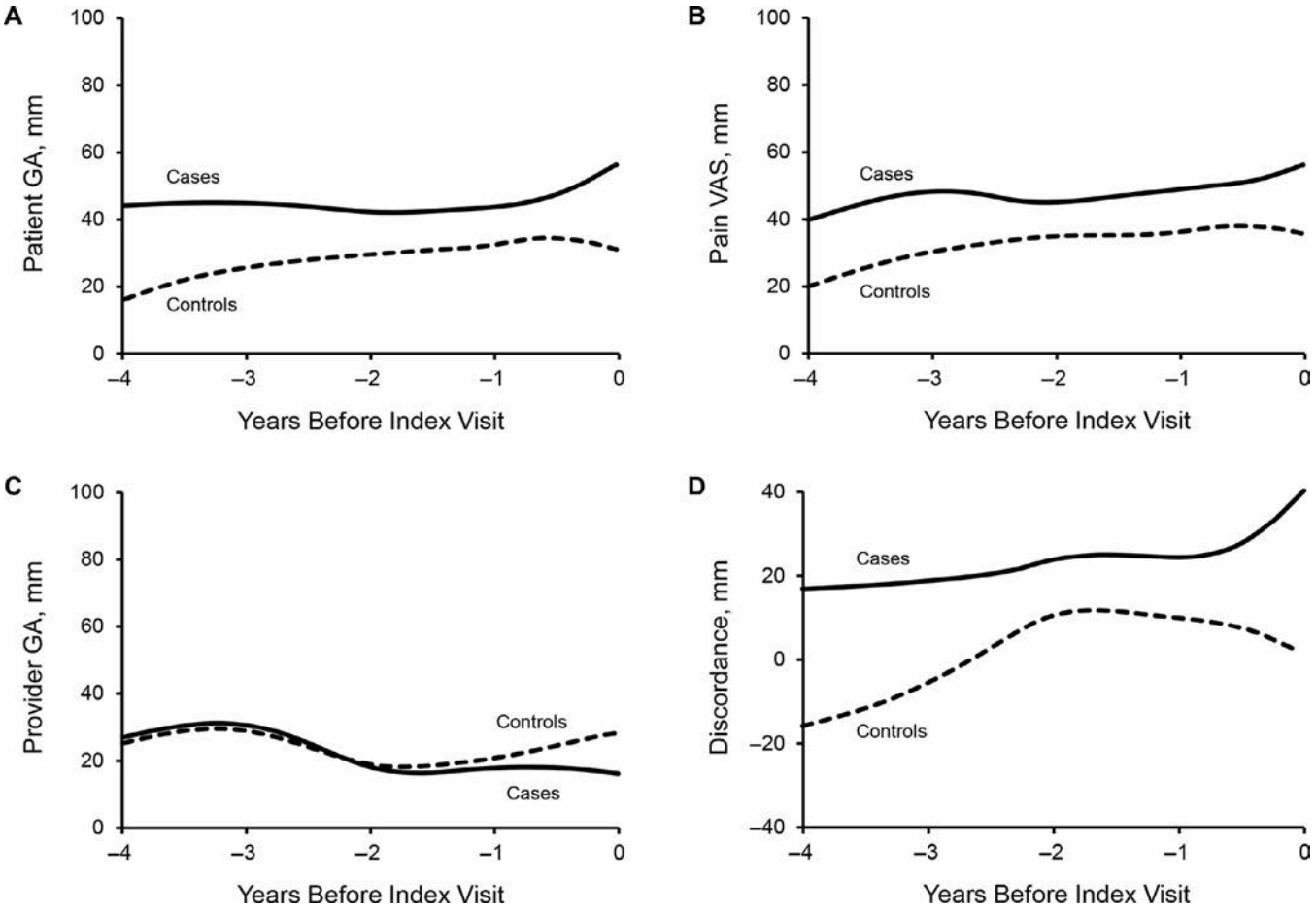

Figure 2. Trends in clinical assessment according to the number of years before the index visit. **A**, Patient global assessment (GA); **B**, Pain visual analog scale (VAS); **C**, Provider GA; **D**, Patient-provider discordance (patient GA minus provider GA). Cases had positive patient-provider discordance; controls had concordance. The values are means.

The mean CDAI score was similar between cases and controls at the index visit because of matching, but at the baseline visit, the CDAI score was higher among cases than controls (Figure 3). On average, over 3 years the CDAI score increased by 2.4 units among controls and decreased by 2.4 units among cases (interaction $P = 0.004$). Pain VAS was consistently higher among cases compared with controls throughout the study period; on average, pain VAS increased by 6 mm among controls and 10 mm among cases over 3 years, but these increases were not significantly different from each other (interaction $P = 0.24$). The tender joint counts did not change over time among the controls but decreased significantly among the cases by 1.4 joints over 3 years (interaction $P = 0.04$), whereas CRP levels increased by 2.7 mg/liter on average over 3 years among controls and did not change significantly among cases (interaction $P = 0.02$). No significant differences in mean levels or rates of change were noted between cases and controls for the swollen joint count or HAQ-II.

Predictors of discordance. Baseline predictors of future discordance were the patient global assessment (odds ratio [OR] 1.41 per 10-unit increase [95% confidence interval (95% CI) 1.20–1.64]), pain VAS (OR 1.26 per 10-unit increase [95% CI 1.11–1.44]), and the CDAI score (OR 1.72 per 12-unit increase [95% CI 1.04–2.85]). ANA positivity was associated with higher odds of future occurrence of discordance (Table 2). Use of methotrexate during the first 6 months of diagnosis was also associated with higher odds of discordance. Previous use of antidepressants (OR 2.87 [95% CI 1.21–6.80]) or fibromyalgia medications (OR 3.20 [95% CI 1.17–8.74]) was significantly associated with discordance. Clinical diagnoses of fibromyalgia (OR 2.14 [95% CI 0.74–5.26]) or depression (OR 1.94 [95% CI 1.02–3.71]) were associated with discordance, while previous use of nonsteroidal antiinflammatory drugs and initiation or modification of treatment with conventional or biologic DMARDs were not statistically significant. Radiographic evidence of erosions was associated with lower odds for the occurrence of discordance (OR 0.43 [95% CI 0.22–0.83]).

Impact of discordance on treatment decisions. No differences were identified between cases and controls in the cumulative numbers of additions or modifications of the DMARD regimen (77% versus 75%) or in treatment with conventional or

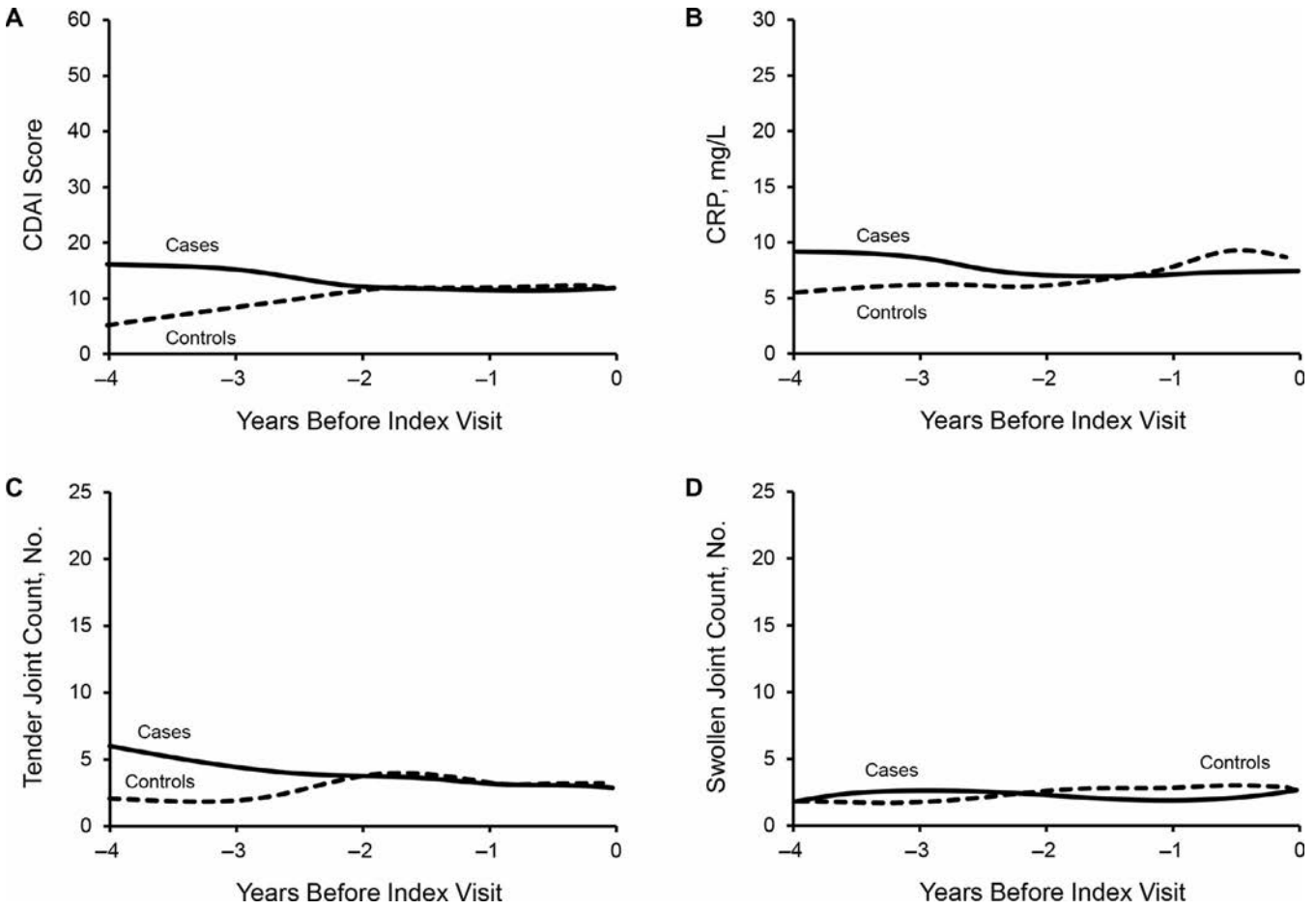

Figure 3. Trends in clinical disease according to the number of years before the index visit. **A**, Clinical Disease Activity Index (CDAI) score; **B**, C-reactive protein (CRP) level; **C**, Tender joint count; **D**, Swollen joint count. Cases had positive patient-provider discordance; controls had concordance. The values are means.

biologic DMARDs between cases with positive patient-provider discordance and controls (data not shown; all $P > 0.05$). Further analysis of treatment changes adjusted for disease activity level at the time of the decision did not reveal significant differences between cases and controls ($P = 0.66$).

DISCUSSION

This study is the first, to our knowledge, to evaluate the evolution of discrepancy between patient and provider global assessments by using electronic health record data collected during routine patient care. The cases were patients with positive patient-provider discordance in our previous cross-sectional study; the controls, with patient global assessments that were concordant with the provider global assessments, were selected from the same study population. This innovative approach enabled us to identify predictors of future positive discordance according to data collected earlier in the disease course. The findings provide new information that illuminates several factors that may contribute to the development of patient-provider discordance.

First, the findings show how discordance between patients and their health care providers evolves during the disease course. The patients with positive discordance at the index visit tended to have persistently higher global assessments compared with the provider global assessment for 3 to 4 years before the index visit. Both the percentages and the rates of discordant visits were significantly higher for cases than for controls before the index visit. Analysis of the trends in discordance over time (Figure 2) suggested that the determinants of discordance were already present earlier in the disease course, although there is evidence of discordance accentuation in the 6 to 12 months before the index date.

Second, and of key importance, the results suggested that cases with discordance have higher clinical disease activity than controls during the 3 to 4 years before the index visit according to the CDAI score and its individual components (Table 1 and Figure 3). Matching by CDAI category was done to minimize confounding by absolute composite disease activity states at the index visit. Considering the potential for circularity in the use of the baseline CDAI score (which incorporates the patient and

provider global assessments) to predict the patient-provider discordance at the index visit, we also analyzed data for the DAS28-CRP, which contains neither the patient global assessment nor the provider global assessment but does include the CRP result. The finding of a higher mean DAS28-CRP and a higher proportion of patients with moderate or high disease activity at baseline (according to DAS28-CRP) mirrored the findings for the CDAI score. Higher disease activity translated into higher HAQ-II physical disability at the baseline visit. The CRP and ESR values at baseline were also higher numerically for cases than for controls, although the differences were not statistically significant. Overall, the patterns showed more inflammatory disease activity in cases than in controls preceding the development of patient-provider discordance, rather than higher CDAI scores due solely to the higher patient global assessment. The elevations of the disease activity measures for cases trended downward and matched the disease activity for the controls by 2 years after the baseline visit. In contrast, the pain and HAQ-II disability scores trended upward among cases with discordance during the time before the index visit. These findings suggest that gaps in the detection of disease activity and the treat-to-target strategy may in some way undergird the development of patient-provider discordance.

We can only speculate on possible explanations for these findings. Persistence of inflammatory disease activity that is either unrecognized by the provider or has responded inadequately to DMARD therapy could contribute to structural joint damage, to secondary degenerative disease, or to the development of peripheral or central pain sensitization later in the disease course. Previous studies have clearly shown that pain is the most important correlate of positive discordance (5), and fibromyalgia has been shown to be an important correlate of discordance in this study population (13). Any of these outcomes could contribute to a scenario in which the patient's symptoms are not directly caused by inflammation and would be less likely to respond to treatment with DMARDs. Lack of improvement despite appropriate DMARD therapy could be expected to cause uncertainty in the clinician's mind and contribute to the provider global assessment being lower than the patient global assessment (20).

Third, the association between positive discordance and lack of radiographic evidence of joint erosions earlier in the disease course is an important finding because it suggests that factors associated with nonerosive disease contribute to the development of patient-provider discordance. The nature of these factors is unclear, but provider bias created by the awareness of nonerosive disease may be a factor. The presence of erosions has been previously defined by both the ACR and EULAR as a feature that carries a poor prognosis (6,7). This association could be a contrast effect: the provider's knowledge of the absence of erosions creates a mindset, or bias, that the patient has mild disease in contrast to other patients who have joint erosions and severe disease; hence, the provider is more likely to assess the disease activity as low despite the patient's view that the disease activity is high (i.e., positive discordance).

Fourth, and unexpectedly, ANA positivity was a predictor of positive discordance in this study. It seems unlikely that this association could be explained by misdiagnosis of RA in patients who truly have systemic lupus erythematosus or other connective tissue diseases. Among patients with RA, ANA positivity is associated with a unique genetic profile (21), and among healthy patients, the presence of ANA and other autoantibodies is associated with the interferon signature, despite the absence of features of overt systemic lupus erythematosus (22). ANA positivity is predictive of an inadequate response to tumor necrosis factor inhibitor therapy among patients with RA (23,24), and this treatment nonresponse may be mediated by increased interferon-β activity (25). These findings underscore the known heterogeneity in the pathophysiology of RA and the need to better stratify patients according to dominant immunologic mechanisms, which would facilitate precision medicine. Ultimately, improved tailoring of treatment to the underlying immunopathogenesis could lead to better health outcomes for patients.

Fifth, the current study highlights the impact of various comorbidities on the development of patient-provider discordance. Previous studies have shown that positive discordance is associated with concurrent and historical depression and fibromyalgia (2,13,26). The temporal course of these comorbidities is not clear from our findings. If future studies further track the evolution of these concomitant disorders, clinicians will better understand the pathogenesis and be able to devise preventive strategies.

Finally, the results of this study suggest that discordance does not affect the decision to modify DMARD therapy. Wolfe and Michaud (27) reported on another type of discordance that was characterized by patients declining to receive intensified treatment with DMARDs in the face of active disease because of their fear of feeling worse or experiencing adverse effects. In the DUO (epidemiologic study of treatment decision in RA: doctor-reported outcomes and patient-reported outcomes) study by Dougados et al (28), DMARD intensification was predominantly based on patient factors. Patients with low-to-moderate disease activity reportedly often felt no need to change therapy unless they were considerably affected by their current disease state (29). The most likely explanation is that the patients' disease experiences are currently not well integrated into shared decision-making about treatment options. Further work is necessary to integrate patient-reported outcomes into systems of rheumatologic care and medical decision-making, particularly when positive discordance exists.

Potential limitations of the current study, which was performed at a single academic center, include its retrospective observational design, which precludes assessment of causation between the baseline factors and later discordance. Patients and providers inherently differ in how they assess the disease, representing a challenge to establishing concordant assessments of global disease activity. Although patients generally return to see the same provider in our practice, patients

may occasionally have been seen by different providers at follow-up, which could have confounded the analysis of the longitudinal changes in patient-provider discordance. CDAI and DAS28-CRP data were missing at baseline for some patients, but it is reassuring that the degree of missing data was similar for cases and controls. Data from the time of RA diagnosis were not available for all patients, limiting our ability to make inferences about the development of discordance during the early stage of the disease. Although patient education, health literacy, socioeconomic status, provider characteristics, and patient-physician communication are all related to discordance, they were not assessed in this study. Finally, the racial and ethnic homogeneity of the study population may limit generalizability to more diverse populations.

In conclusion, the time course for the development of positive discordance indicates that some of the determinants of discordance are present earlier in the disease course. The findings provide evidence of practice gaps in the diagnosis and treat-to-target strategy of inflammatory disease activity (particularly among patients with nonerosive disease) and of comorbidities (particularly depression and fibromyalgia) that lead to patient-provider discordance. The findings of this study suggest that abrogation of the inflammatory activity of RA and management of associated comorbidities such as depression and fibromyalgia might help reduce patient-provider discordance. Future studies are needed to identify the mechanisms by which ANA-positive status without a clinical diagnosis of connective tissue disease contributes to a greater likelihood of future discordance.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Davis had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Challa, Kvrgic, Crowson, Davis.

Acquisition of data. Challa, Kvrgic, Crowson, Matteson, Mason, Michet, Schaffer, Wright, Davis.

Analysis and interpretation of data. Challa, Kvrgic, Crowson, Davis.

REFERENCES

1. Castrejón I, Yazici Y, Samuels J, Luta G, Pincus T. Discordance of global estimates by patients and their physicians in usual care of many rheumatic diseases: association with 5 scores on a Multidimensional Health Assessment Questionnaire (MDHAQ) that are not found on the Health Assessment Questionnaire (HAQ). Arthritis Care Res (Hoboken) 2014;66:934–42.
2. Barton JL, Imboden J, Graf J, Glidden D, Yelin EH, Schillinger D. Patient-physician discordance in assessments of global disease severity in rheumatoid arthritis. Arthritis Care Res (Hoboken) 2010;62:857–64.
3. Khan NA, Spencer HJ, Abda E, Aggarwal A, Alten R, Ancuta C, et al. Determinants of discordance in patients' and physicians' rating of rheumatoid arthritis disease activity. Arthritis Care Res (Hoboken) 2012;64:206–14.
4. Nicolau G, Yogui MM, Vallochi TL, Gianini RJ, Laurindo IM, Novaes GS. Sources of discrepancy in patient and physician global assessments of rheumatoid arthritis disease activity. J Rheumatol 2004;31:1293–6.
5. Desthieux C, Hermet A, Granger B, Fautrel B, Gossec L. Patient-physician discordance in global assessment in rheumatoid arthritis: a systematic literature review with meta-analysis. Arthritis Care Res (Hoboken) 2016;68:1767–73.
6. Smolen JS, Breedveld FC, Burmester GR, Bykerk V, Dougados M, Emery P, et al. Treating rheumatoid arthritis to target: 2014 update of the recommendations of an international task force. Ann Rheum Dis 2016;75:3–15.
7. Singh JA, Saag KG, Bridges SL Jr, Akl EA, Bannuru RR, Sullivan MC, et al. 2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. Arthritis Care Res (Hoboken) 2016;68:1–25.
8. Smolen JS, Strand V, Koenig AS, Szumski A, Kotak S, Jones TV. Discordance between patient and physician assessments of global disease activity in rheumatoid arthritis and association with work productivity. Arthritis Res Ther 2016;18:114.
9. Karpouzas GA, Ramadan SN, Cost CE, Draper TL, Hernandez E, Strand V, et al. Discordant patient-physician assessments of disease activity and its persistence adversely impact quality of life and work productivity in US Hispanics with rheumatoid arthritis. RMD Open 2017;3:e000551.
10. Studenic P, Radner H, Smolen JS, Aletaha D. Discrepancies between patients and physicians in their perceptions of rheumatoid arthritis disease activity. Arthritis Rheum 2012;64:2814–23.
11. Kaneko Y, Kuwana M, Kondo H, Takeuchi T. Discordance in global assessments between patient and estimator in patients with newly diagnosed rheumatoid arthritis: associations with progressive joint destruction and functional impairment. J Rheumatol 2014;41:1061–6.
12. Furu M, Hashimoto M, Ito H, Fujii T, Terao C, Yamakawa N, et al. Discordance and accordance between patient's and physician's assessments in rheumatoid arthritis. Scand J Rheumatol 2014;43:291–5.
13. Challa DN, Kvrgic Z, Cheville AL, Crowson CS, Bongartz T, Mason TG Jr, et al. Patient-provider discordance between global assessments of disease activity in rheumatoid arthritis: a comprehensive clinical evaluation. Arthritis Res Ther 2017;19:212.
14. Ward MM, Guthrie LC, Alba MI. Standards of comparison and discordance in rheumatoid arthritis global assessments between patients and clinicians. Arthritis Care Res (Hoboken) 2017;69:1260–5.
15. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO III, et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum 2010;62:2569–81.
16. Wolfe F, Michaud K, Pincus T. Development and validation of the health assessment questionnaire II: a revised version of the health assessment questionnaire. Arthritis Rheum 2004;50:3296–305.
17. Aletaha D, Smolen JS. The Simplified Disease Activity Index and Clinical Disease Activity Index to monitor patients in standard clinical care. Rheum Dis Clin North Am 2009;35:759–72.
18. Inoue E, Yamanaka H, Hara M, Tomatsu T, Kamatani N. Comparison of Disease Activity Score (DAS)28- erythrocyte sedimentation rate and DAS28- C-reactive protein threshold values. Ann Rheum Dis 2007;66:407–9.
19. Prevoo ML, van 't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight–joint counts: development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum 1995;38:44–8.
20. Cleanthous S, Newman SP, Shipley M, Isenberg DA, Cano SJ. What constitutes uncertainty in systemic lupus erythematosus and rheumatoid arthritis? Psychol Health 2013;28:171–88.

21. Liao KP, Kurreeman F, Li G, Duclos G, Murphy S, Guzman R, et al. Associations of autoantibodies, autoimmune risk alleles, and clinical diagnoses from the electronic medical records in rheumatoid arthritis cases and non–rheumatoid arthritis controls. Arthritis Rheum 2013;65:571–81.
22. Wither J, Johnson SR, Liu T, Noamani B, Bonilla D, Lisnevskaia L, et al. Presence of an interferon signature in individuals who are antinuclear antibody positive lacking a systemic autoimmune rheumatic disease diagnosis. Arthritis Res Ther 2017;19:41.
23. Hagiwara S, Tsuboi H, Honda F, Takahashi H, Kurata I, Ohyama A, et al. Association of anti-Ro/SSA antibody with response to biologics in patients with rheumatoid arthritis. Mod Rheumatol 2016;26:857–62.
24. Salgado E, Maneiro JR, Gomez-Reino JJ. Predictors of response to TNF antagonists. Curr Pharm Des 2015;21:221–32.
25. Wampler Muskardin T, Vashisht P, Dorschner JM, Jensen MA, Chrabot BS, Kern M, et al. Increased pretreatment serum IFN-β/α ratio predicts non-response to tumour necrosis factor alpha inhibition in rheumatoid arthritis. Ann Rheum Dis 2016;75:1757–62.
26. Pollard LC, Kingsley GH, Choy EH, Scott DL. Fibromyalgic rheumatoid arthritis and disease assessment. Rheumatology (Oxford) 2010;49:924–8.
27. Wolfe F, Michaud K. Resistance of rheumatoid arthritis patients to changing therapy: discordance between disease activity and patients' treatment choices. Arthritis Rheum 2007;56:2135–42.
28. Dougados M, Nataf H, Steinberg G, Rouanet S, Falissard B. Relative importance of doctor-reported outcomes vs patient-reported outcomes in DMARD intensification for rheumatoid arthritis: the DUO study. Rheumatology (Oxford) 2013;52:391–9.
29. Fraenkel L, Seng EK, Cunningham M, Mattocks K. Understanding how patients (vs physicians) approach the decision to escalate treatment: a proposed conceptual model. Rheumatology (Oxford) 2015;54:278–85.

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Tender Joint Count and Inflammatory Activity in Patients With Established Rheumatoid Arthritis: Results From a Longitudinal Study

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Objective. The tender joint count (TJC) is included in composite disease activity scores (CDAS) (the Disease Activity Score in 28 joints, the Clinical Disease Activity Index, and the Simplified Disease Activity Index). The impact of having predominantly tender joints was explored by use of the Tender-Swollen Joint Count Difference (TSJD), and ultrasound (US) provided a measure of joint inflammation. The current study aimed to explore the cross-sectional and longitudinal associations between the TSJD and a spectrum of outcome measures, including US scores in patients with established rheumatoid arthritis (RA) during follow-up and while receiving treatment with biologic disease-modifying antirheumatic drugs (bDMARDs).

Methods. This was an observational study of 209 patients with established RA consecutively included upon initiation of bDMARD treatment and followed-up with clinical, laboratory, and comprehensive US examinations at 0, 1, 2, 3, 6, and 12 months. Patients were categorized into 2 groups: those with predominantly tender joints (TSJD >0) and those with predominantly swollen joints (TSJD ≤0). Statistical analyses included Pearson's correlation coefficient, an independent samples *t*-test, and regression analyses.

Results. The TJC had high correlations only with patient-reported outcomes (PROMs) ($P < 0.001$). Levels from CDAS and PROMs were significantly higher ($P < 0.001$) at all visits in patients with TSJD >0 compared to those with TSJD <0. Laboratory markers and assessor's global visual analog scale scores were similar, and US sum scores were significantly lower ($P < 0.001$–0.03). The baseline TSJD positively predicted levels of all CDAS at 6 months ($P < 0.001$–0.019) but was a negative predictor of US sum scores (gray-scale and power Doppler) at 6 and 12 months ($P < 0.001$).

Conclusion. Patients with predominantly tender joints had higher CDAS but lower levels of inflammation as defined by US. These findings indicate that inclusion of the TJC in the CDAS may contribute to misleading information about inflammatory activity.

INTRODUCTION

Remission is the treatment target in the era of improved and effective medication for patients with rheumatoid arthritis (RA). The most commonly used composite disease activity scores (CDAS) include both the tender joint count (TJC) and the swollen joint count (SJC) (1–3), e.g., the Disease Activity Score including 28 joints (DAS28) (4), the Clinical Disease Activity Index (CDAI) (5), the Simplified Disease Activity Index (SDAI) (6), as well as the American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) definition of remission (7).

Assessment of the SJC has high face validity in patients with RA, while the value of including the TJC in CDAS may not be so apparent. Tender joint assessment is part of a routine examination,

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SIGNIFICANCE & INNOVATIONS

- The tender joint count (TJC) was highly associated with subjective assessments but not with ultrasound (US) scores.
- Patients with predominantly tender joints had higher clinical composite score levels but lower US scores.
- The TJC had low association with objective assessments of inflammation.

but even if there is agreement on how strong the assessor should press on joints (8), this may not be included in a routine setting, and there is no consensus on where the assessor should exert pressure on each joint. The patient may perceive a joint as tender when inflammation causes an increase of pain fiber innervation and activity, leading to hyperalgesia (9). However, tenderness may also be caused by damage in the joint, as in the case of secondary osteoarthritis or subluxation, and cause nociception even if the RA inflammation is no longer present. Long-lasting activation of pain signals from the joint may cause central sensitization in the medulla with increased pain despite lack of ongoing inflammation (10,11). A higher number of tender versus swollen joints is found in ~15–20% of patients with RA who additionally have fibromyalgia (12–17). There is limited knowledge concerning predictors of chronic pain development in RA, but long-lasting nociceptive input, as well as psychological factors such as anxiety, depression, and catastrophizing, seem to be associated (18,19). Thus, the TJC has a multifactorial basis and may not always reflect ongoing inflammation.

Ultrasonography (US) is increasingly used by rheumatologists to assess the degree of inflammatory activity in joints and tendons in patients with RA (20–22). Synovitis is scored by use of changes in gray-scale (GS) and degree of vascularization by use of power Doppler (PD). US has been shown to be strongly associated with synovitis detected by magnetic resonance imaging (MRI) (23,24), and a high intrareader and interreader reliability of synovitis scoring has been demonstrated (25,26).

A few studies have explored the predictive value of discordance between TJC and SJC and its effect on the likelihood of remission in RA, while having predominantly tender joints has been shown to be associated with a reduced likelihood of CDAS remission at follow-up (27,28). CDAS are thought to be proxies for degree of inflammation and are recommended as measures of disease activity in treat-to-target strategies (29). However, in light of the multifactorial causes of joint tenderness, there is a need for deeper understanding of tender joints as a measure of inflammation. A comprehensive US assessment may be the examination that most closely reflects the actual inflammatory activity.

The current study proceeded from a previously published study of a cohort of patients with RA who had begun treatment with biologic disease modifying anti-rheumatic drugs (bDMARDs) (30) and includes comprehensive longitudinal data collection, including US. The impact of tender joints was explored by use of the Tender-Swollen Joint Count Difference (TSJD), and the main objectives were to explore and compare the associations between the TSJD, patient-reported outcome measures (PROMs), clinical assessments, and US scores using US as a gold standard comparator to define the actual status of inflammation. Furthermore, we examined how the baseline TSJD predicted CDAS and US levels as well as CDAS and US remission during follow-up.

PATIENTS AND METHODS

In this longitudinal observational study, patients with RA who met the ACR 1987 revised criteria for the classification of rheumatoid arthritis (31) were consecutively included in the study when they initiated or switched bDMARD treatment. The patients were assessed at baseline and after 1, 2, 3, 6, and 12 months, as previously described (30). The study was approved by the Norwegian Regional Committee for Medical and Health Research Ethics South East, and the patients gave written informed consent according to the Declaration of Helsinki.

CDAS. The following CDAS were calculated for each visit: DAS28 with erythrocyte sedimentation rate (DAS28-ESR) (0.56*√(tender joints) + 0.28* √(swollen joints) + 0.70*Ln(ESR) + 0.014*(patient's global visual analog scale [VAS 0–100]) (4); the CDAI (sum of 28 TJCs and 28 SJCs, the patient's global VAS [0–10] and the assessor's global VAS [0–10]) (5); the SDAI (CDAI with the addition of C-reactive protein [CRP] level in mg/dl) (6); and the ACR/EULAR Boolean remission criteria (number of tender and swollen joints, patient's global VAS [0–10], and CRP level mg/dl, all ≤1) (7).

Patient-reported outcome measures. The patients scored joint pain during the last week of the study and their global assessment of disease on a VAS. Functional ability was assessed by the Modified Health Assessment Questionnaire (M-HAQ) (32). The Rheumatoid Arthritis Impact of Disease (RAID) score was also included (33). This instrument calculates the total score based on 7 items (pain, physical function, fatigue, physical well-being, sleep disturbances, emotional well-being, and coping), each one assessed according to a numeric rating scale with a range from 0 to 10. Two questions from the Coping Strategies Questionnaire (30,34) were used to assess pain catastrophizing. These questions have been found to be strongly associated with the original complete questionnaire and provide an adequate valid estimate of the pain catastrophizing domain (35,36).

Clinical and laboratory assessments. Two trained study nurses blinded to the US results performed 28 TJC/SJCs and the assessor's global VAS. ESR (mm/hour) and CRP level (mg/liter) were examined as part of the hospital routine.

Table 1. Baseline characteristics of the patients with established rheumatoid arthritis (n = 209)*

Variable (range)	Mean ± SD	Median (IQR)
No. of tender joints (0–28)	5.7 ± 6.1	4 (1–9)
No. of swollen joints (0–28)	6.3 ± 5.1	5 (2–10)
Joint pain VAS (0–100)	45.1 ± 27.0	41 (24–68)
Patient's global VAS (0–100)	49.1 ± 26.8	50 (26–71)
Pain catastrophizing (0–6)	2.2 ± 1.5	2.5 (1–3)
M-HAQ score (0–3)	0.66 ± 0.56	0.5 (0.25–1.0)
RAID score (0–10)	4.5 ± 2.3	4.5 (2.6–6.3)
Assessor's global VAS (0–100)	30.0 ± 15.5	27 (20–37)
ESR mm/hour	28.1 ± 21.6	24 (12–37)
CRP level mg/liter	12.9 ± 18.9	6 (2–15)
DAS28	4.5 ± 1.5	4.5 (3.6–5.5)
CDAI (0–76)	20.0 ± 11.8	16.8 (11.3–26.6)
SDAI (0–86)	21.2 ± 12.5	18.4 (12.3–28.4)
Sum score GS (0–120)	30.0 ± 18.9	26 (16–41)
Sum score PD (0–120)	14.2 ± 13.6	10 (3–21)

* IQR = interquartile range; VAS = visual analog scale; M-HAQ = modified Health Assessment Questionnaire; RAID = Rheumatoid Arthritis Impact of Disease questionnaire; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; DAS28 = Disease Activity Score including 28 joints; CDAI = Clinical Disease Activity Index; SDAI = Simplified Disease Activity Index; GS = gray-scale; PD = power Doppler.

Ultrasound assessments. An experienced sonographer (HBH) performed all the US examinations (Siemens Antares Excellence version, 5–13 MHz probe optimized with GS frequency of 11.3 MHz, PD frequency 7.3 MHz, and PRF of 391 Hz) and had no access to the clinical assessments or laboratory markers from the same time point, nor to previous US results. GS and PD were scored semi-quantitatively on a 4-point scale (where 0 = no, 1 = minor, 2 = moderate, 3 = major presence) of 36 joints (bilateral wrist [radiocarpal, midcarpal, and radioulnar joints scored separately], metacarpophalangeal 1–5, proximal interphalangeal 2–3, elbow, knee, ankle [tibiotalar], and metatarsophalangeal 1–5) with the Norwegian US atlas as reference (25), as well as 4 tendon sheaths (bilateral extensor carpi ulnaris and tibialis posterior). Sum scores were calculated separately for GS and PD, including the sum of scores for all 36 joints and 4 tendons. The sonographer has previously shown high intrareader reliability for US assessments of these joints and tendons (weighted kappa values of 0.83–0.88 for GS and PD) (25,37). Since there is no consensus on how to define US remission, we presently explored several PD remission criteria, including the sum score of zero (38) as well as the sum score of 1, 2, or 3.

Statistical analysis. Pearson's correlations were used with the following definitions of correlation coefficients: negligible <0.2, weak 0.2 to 0.39, moderate 0.40 to 0.59, strong 0.60 to 0.79, and very strong ≥0.80. TSJD was calculated as the numeric difference between 28 TJCs and 28 SJCs. To explore the influence of TSJD on group level, the patients were categorized into 2 groups at all study visits: TSJD >0 (i.e., patients with predominantly tender joints) and TSJD ≤0 (i.e., patients with predominantly swollen joints). In addition, we divided the patients into a fibromyalgic RA (FM-RA) group, as described by Pollard et al based on TSJD ≥7, and a non–FM-RA group with TSJD ≤6 (17). These groups were compared by use of independent sample *t*-tests, except for when we used the Mann-Whitney test to compare the non-completer group with completers.

Linear regression analyses were performed to explore associations between baseline TSJD (adjusting for age, sex, and disease duration) and each of the different CDAS or GS/PD sum scores at 6 or 12 months. Logistic regression was used to explore the predictive value of baseline TSJD (adjusted for age, sex, and disease duration) for achievement of remission defined by the CDAS or PD sum score remission criteria at 6 or 12 months. The last observation carried forward replaced missing data during follow-up (<5% of the different variables). All analyses were performed using SPSS version 21 software, and *P* values less than 0.05 were considered statistically significant.

RESULTS

Patient characteristics have been described previously (30). In short, a total of 209 patients (81% women, mean ± SD age 53.3 ± 13.2 years, mean ± SD disease duration 10.0 ± 8.8 years, 79.2% anti–cyclic citrullinated peptide positive, and 68.6% positive for rheumatoid factor) were consecutively included. A total of 152 patients (72.7%) completed a 12-month follow-up. Mean ± SD and median (interquartile range [IQR]) of baseline variables are shown in Table 1. All patients initiated and continued treatment with the following bDMARDs: etanercept (34.9%), rituximab (20.6%), certolizumab (11.0%), infliximab (10.0%), tocilizumab (8.6%), adalimumab (6.7%), golimumab (5.3%), or abatacept (2.9%). In addition, 83.6% received co-medication with synthetic DMARDs (90.6% of these received methotrexate), and at baseline 55.0% also received prednisolone (mean ± SD dose of 8.0 ± 5.3 mg). At baseline, mean ± SD/median (IQR) of the TSJD was 4.9 ± SD 4.6/3 (IQR 2, 7) for the TSJD >0 group (n = 84) and −4.3 ± SD 4.8/−3 (IQR −1, −6) for the TSJD ≤0 group (n = 125).

A total of 57 patients did not complete the 12-month follow-up. At baseline, the non-completers had significantly higher patient global VAS (*P* = 0.03), pain catastrophizing (*P* = 0.04), and RAID score (*P* = 0.003), but group differences were not significant for other variables, including TSJD, laboratory markers, CDAS, or US scores.

Cross-sectional analyses. *Correlations between individual variables during follow-up*. Table 2 shows the median (range) cross-sectional correlation coefficients of variables included in CDAS as well as US sum scores at all visits. The TJC was

Table 2. Median (range) of the cross-sectional Pearson's correlation coefficients at baseline (n = 209), 1 month (n = 209), 2 months (n = 205), 3 months (n = 198), 6 months (n = 184), and 12 months (n = 152) between variables included in the different composite disease activity scores along with ultrasound sum scores*

	SJC		TJC		Global VAS, patient		Global VAS, assessor		ESR		CRP level		Sum score GS	
	Median	(Range)	Median	(Range)	Median	(Range)	Median	(Range)	Median	(Range)	Median	(Range)	Median	(Range)
TJC	0.37†	(0.33–0.41)												
Patient's global VAS	0.21‡	(0.20–0.25)	0.59†	(0.45–0.63)										
Assessor's global VAS	0.81†	(0.77–0.86)	0.43†	(0.38–0.46)	0.42†	(0.35–0.45)								
ESR	0.33†	(0.26–0.43)	0.23†	(0.21–0.32)	0.28†	(0.17–0.32)	0.49†	(0.45–0.58)						
CRP	0.26†	(0.24–0.34)	0.14	(0.09–0.17)	0.23†	(0.14–0.29)	0.43†	(0.38–0.49)	0.68†	(0.44–0.71)				
Sum score GS	0.75†	(0.71–0.79)	0.14	(0.10–0.18)	0.07	(0.05–0.13)	0.65†	(0.63–0.70)	0.30†	(0.24–0.33)	0.30†	(0.24–0.36)		
Sum score PD	0.76†	(0.68–0.82)	0.16‡	(0.08–0.25)	0.14	(0.05–0.18)	0.69†	(0.64–0.72)	0.36†	(0.35–0.40)	0.32†	(0.26–0.39)	0.86†	(0.85–0.90)

* Values are median (range) correlation coefficients. SJC = swollen joint count; TJC = tender joint count; VAS = visual analog scale; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; GS = gray-scale; PD = power Doppler.
† $P \leq 0.001$.
‡ $P \leq 0.05$.

Table 3. Mean values during follow-up of the patient-reported outcome measures, composite scores, and laboratory and ultrasound assessments divided into groups depending on TSJD*

	Baseline		1 month		2 months		3 months		6 months		12 months	
	TSJD >0/TSJD ≤0	*P*	TSJD >0/TSJD ≤0	*P*	TSJD >0/TSJD ≤0	*P*	TSJD >0/TSJD ≤0	*P*	TSJD >0/TSJD ≤0	*P*	TSJD >0/TSJD ≤0	*P*
No. of patients	84/125		79/130		69/136		60/138		57/127		47/105	
Joint pain VAS	53.6/39.3†	<0.001†	45.3/22.5†	<0.001†	41.4/19.3†	<0.001†	37.1/17.7†	<0.001†	33.7/17.0†	<0.001†	32.9/17.3†	<0.001†
Patient's global VAS	58.7/42.5†	<0.001†	48.6/25.5†	<0.001†	44.2/21.4†	<0.001†	42.9/19.0†	<0.001†	37.4/18.3†	<0.001†	35.8/19.6†	<0.001†
Pain catastro-phizing	2.6/2.0†	0.002†	2.6/1.5†	<0.001†	2.4/1.4†	<0.001†	2.3/1.3†	<0.001†	2.0/1.3†	0.016†	1.7/1.2†	0.015†
M-HAQ score	0.83/0.55†	0.001†	0.71/0.33†	<0.001†	0.81/0.30†	0.011†	0.65/0.27†	<0.001†	0.56/0.30†	0.004†	0.50/0.32†	0.026†
RAID score	5.3/3.9†	<0.001†	4.8/2.6†	<0.001†	4.3/2.4†	<0.001†	4.1/2.1†	<0.001†	3.7/2.0†	<0.001†	3.6/2.2†	<0.001†
DAS28	5.2/4.1†	<0.001†	4.7/3.4†	<0.001†	4.6/3.1†	<0.001†	4.5/3.0†	<0.001†	4.0/2.8†	<0.001†	3.8/2.7†	<0.001†
CDAI	23.8/17.4†	<0.001†	20.0/13.0†	<0.001†	19.0/11.0†	<0.001†	18.7/9.6†	<0.001†	14.2/8.7†	0.001†	12.8/8.2†	0.005†
SDAI	25.1/18.6†	<0.001†	20.9/13.9†	<0.001†	19.7/11.7†	<0.001†	19.3/10.1†	<0.001†	14.7/9.1†	0.002†	13.1/8.8†	0.011†
ESR	29.8/26.9	NS	24.3/21.4	NS	21.5/19.8	NS	22.9/17.9	NS	18.6/16.9	NS	17.0/17.1	NS
CRP level	13.5/12.5	NS	9.2/8.1	NS	6.4/7.1	NS	6.0/5.3	NS	5.0/4.6	NS	2.6/5.5‡	0.018‡
Assessor's global VAS	28.9/30.7	NS	23.2/23.0	NS	20.4/19.8	NS	18.5/17.4	NS	15.9/16.2	NS	14.8/15.8	NS
Sum score GS	24.3/33.8‡	<0.001‡	21.5/29.2‡	0.001‡	20.3/27.4‡	0.002‡	18.3/23.9‡	0.01‡	16.1/23.3‡	<0.001‡	14.8/21.8‡	0.001‡
Sum score PD	10.0/17.0‡	<0.001‡	8.2/12.8‡	0.003‡	7.6/11.3‡	0.017‡	6.6/9.7‡	0.03‡	5.2/8.7‡	0.007‡	3.5/7.3‡	<0.001‡

* TSJD = tender-swollen joint count difference; VAS = visual analog scale; M-HAQ = modified Health Assessment Questionnaire; RAID = Rheumatoid Arthritis Impact of Disease questionnaire; DAS28 = Disease Activity Score including 28 joints; CDAI = Clinical Disease Activity Index; SDAI = Simplified Disease Activity Index; ESR = erythrocyte sedimentation rate; NS = not significant; CRP = C-reactive protein; GS = gray-scale; PD = power Doppler.
† Significantly higher levels for the patients with predominantly tender joints (TSJD >0) compared to predominantly swollen joints (TSJD ≤0).
‡ Significantly lower levels for the patients with predominantly tender joints (TSJD >0) compared to predominantly swollen joints (TSJD ≤0).

moderately to strongly correlated with the patient's global VAS, weakly to moderately correlated with the assessor's global VAS, weakly correlated with the SJC, negligibly to weakly correlated with laboratory markers, and negligibly correlated with US scores, while in contrast, the SJC was strongly correlated with the assessor's global VAS and US scores and weakly correlated with the patient's global VAS scores.

The correlations between the TJC and PROMs were highly significant ($P < 0.001$). The median and range correlation coefficients during follow-up were, for joint pain r = 0.59 (range 0.45–0.62), pain catastrophizing r = 0.40 (range 0.30–0.46), RAID r = 0.61 (range 0.45–0.64), and M-HAQ r = 0.53 (range 0.33–0.63). On the other hand, the SJC had negligible to weak correlations with PROMs, joint pain r = 0.25 (range 0.17–0.27), pain catastrophizing r = 0.12 (range 0.01–0.16), RAID r = 0.20 (range 0.17–0.23), and M-HAQ r = 0.26 (range 0.09–0.29). The TSJD was positively correlated with all the PROMs at all examinations with median and range correlation coefficients of r = 0.35 (range 0.18–0.45; $P = 0.03$ to <0.001) and negatively correlated with GS and PD sum scores during the study, r = –0.47 (range –0.44, –0.54; $P < 0.001$ for all).

Comparison of clinical, laboratory, and US assessments across TSJD groups. All variables, including PROMs, clinical assessments, CDAS, laboratory variables, and US (GS and PD) scores, improved significantly during the study ($P < 0.001$). During follow-up, patients with TSJD >0 versus TSJD ≤0 had significantly higher PROMs and CDAS ($P \leq 0.001$–0.03), while the assessor's global VAS and laboratory variables were similar (except lower levels of CRP level at 12 months, $P = 0.02$). On the other hand, GS and PD sum scores were significantly lower in patients with TSJD >0 compared to patients with TSJD ≤0 ($P \leq 0.001$–0.03) (Table 3). Figure 1 illustrates the differences between the 2 TSJD groups for the patient's global VAS, DAS28, the assessor's global VAS, and sum score PD.

Patients with FM-RA. Only 22 patients (10.5%) fulfilled the FM-RA definition (17) at baseline, and it decreased to 11 (6.0%) at 6 months and 8 (5.3%) at 12 months. During follow-up (6 and 12 months), patients with FM-RA versus those without FM-RA had significantly higher PROMs and CDAS ($P < 0.001$ for all variables at 6 months; $P \leq 0.03$ for all variables at 12 months), whereas the assessor's global VAS, ESR, CRP level, and US scores did not differ between the groups. None of the patients with FM-RA reached remission at 6 or 12 months according to any CDAS. However, the FM-RA group was heterogeneous at all time points, and patients had from low to high levels of objective markers of inflammation (evaluated by the SJC and US sum scores; data not shown).

Longitudinal analyses. *Baseline TSJD as predictor of CDAS and US levels at 6 and 12 months*. Linear regression analyses showed that baseline TSJD was a positive predictor for the level of the DAS28, the CDAI, and the SDAI at 6 months ($P < 0.001$, $P = 0.01$, and $P = 0.02$, respectively) as well as the DAS28 at 12 months ($P = 0.02$). On the other hand, baseline TSJD levels negatively predicted the sum score GS ($P < 0.001$) and PD ($P < 0.001$) at 6 and 12 months.

Baseline TSJD as predictor of CDAS or PD remission at 6 and 12 months. By logistic regression analysis, baseline TSJD levels were not associated with remission according to the CDAS or the ACR/EULAR Boolean definition at 6 or 12 months ($P = 0.2$–1.0). However, the baseline TSJD positively predicted all the different definitions of PD sum score remission at both 6

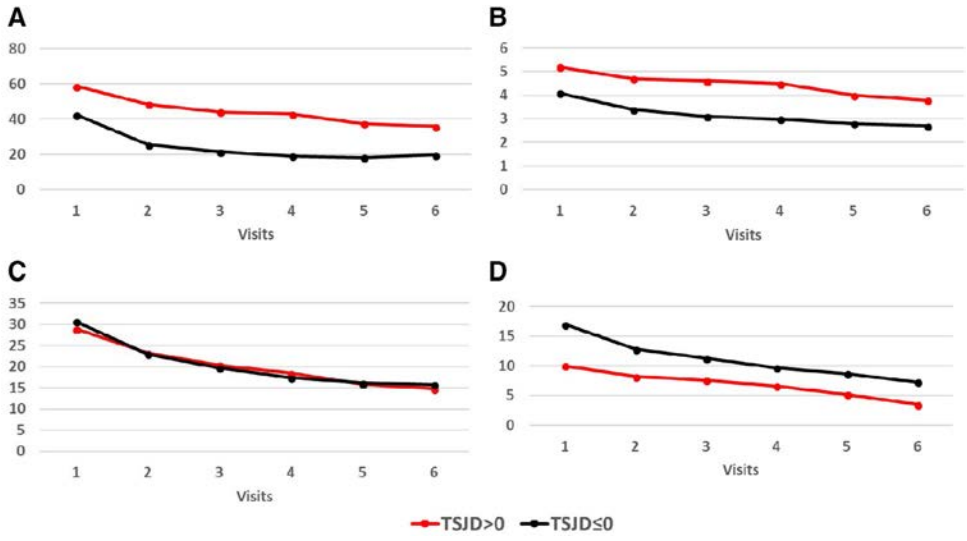

Figure 1. Mean values of different variables during follow-up: **A**, Patient's global visual analog scale (VAS) score; **B**, Disease Activity Score including 28 joints (DAS28); **C**, Assessor's global VAS; **D**, Sum score of power Doppler (PD). Visits are at baseline (1), after 1 month (2), 2 months (3), 3 months (4), 6 months (5), and 12 months (6). Patients were categorized into 2 groups: TSJD >0 and TSJD ≤0 at each visit. Patients with TSJD >0 versus TSJD ≤0 had at all visits significantly higher patient's global VAS and DAS28 ($P < 0.001$), no differences for assessor's global VAS, and a lower sum score of PD ($P \leq 0.001$–0.03). TSJD = tender-swollen joint count difference.

Table 4. Predictive value of baseline TSJD for PD sum scores of remission (different definitions) at 6 and 12 months*

	PD sum score = 0		PD sum score ≤1		PD sum score ≤2		PD sum score ≤3	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
6 months	1.10 (1.02–1.17)	0.010	1.07 (1.01–1.13)	0.024	1.07 (1.02–1.13)	0.012	1.08 (1.03–1.14)	0.003
12 months	1.09 (1.02–1.18)	0.018	1.08 (1.01–1.15)	0.018	1.10 (1.04–1.18)	0.003	1.10 (1.04–1.17)	0.002

* Calculations are by logistic regression with odd ratios. TSJD = tender-swollen joint difference (of 28 assessed joints); PD = power Doppler; OR = odds ratio; 95% CI = 95% confidence interval.

and 12 months (odds ratio 1.07–1.10 [95% confidence interval 1.01–1.18], *P* = 0.002–0.02) (Table 4).

DISCUSSION

In the current study, the number of tender joints was highly associated with PROMs but showed weak or no associations with the more objective assessments of inflammation. The novelty of our study is the inclusion of a comprehensive US assessment as an objective assessment of inflammation. At all visits, patients with predominantly tender joints were found to have lower US-verified synovitis but higher levels of PROMs and CDAS, and the baseline TSJD was shown to be a negative predictor of US sum score levels but a positive predictor of CDAS levels. These results indicate that tender joints do not reflect the same pathology as found with US.

US is frequently used by rheumatologists in clinical practice because it provides a sensitive assessment of inflammatory activity. Several studies have shown US scores to have low or only moderate correlations with CDAS (39–41). In this study, US sum scores were strongly correlated with the SJC but not with the TJC. The association between US scores and swollen joints is supported by previous studies that show US to have comparable sensitivity to MRI for detecting synovitis in joints and tendons (20,24,42). Since PD activity is thought to reflect active inflammation and thus activation of pain fibers, an association with tender joints could also be expected. However, we did not find any correlation between TJC and PD scores. In addition, the TJC had no or only moderate correlation with the SJC, the assessor's global VAS, and laboratory markers of disease activity, which may raise concerns about the use of the TJC in most CDAS for assessment of inflammatory activity.

In the current study, baseline TSJD levels positively predicted CDAS levels, but they did not predict CDAS remission. However, the study by Michelsen et al, which includes 2,735 patients with RA (28), found baseline TSJD to be a negative predictor of CDAS remission. On the other hand, the baseline TSJD was presently a positive predictor of PD remission, which indicates that patients with more tender than swollen joints at baseline tend to have higher levels of CDAS at follow-up but less active inflammation when evaluated with PD.

Pollard et al (17) define patients with at least 7 more tender than swollen joints as patients with FM-RA, and in the current study, this patient group had significantly higher levels of CDAS throughout the study. However, we found FM-RA to include both patients with no or a low degree of US inflammation as well as patients with a high degree of US inflammation. Thus, even if it was a low number of patients with FM-RA, the current study does not support the identification of patients with FM-RA as a group with low inflammatory activity but points to the importance of exploring the background for a high TSJD.

In the current study, 28 joints were assessed for tenderness and compared with a more comprehensive US examination. It could be argued that a similar number of joints should be examined for comparison of the 2 methods. However, our objective was to explore tender joints as used in the different CDAS with the use of US as a gold standard for inflammatory activity. Thus, we used a comprehensive US examination to obtain more information about the inflammatory status.

The major strength of the current study is the longitudinal design, including a comprehensive clinical and US evaluation. Further strengths are the clinical joint assessments performed by only 2 trained nurses and the expertise of the sonographer. The 2 study nurses had >10 years of experience and had similar training in clinical joint examinations; however, we did not assess their reliability on joint evaluations. The major limitations include performance in only 1 center, which may limit the generalizability of the results, as well as the inclusion of only patients with established RA, who may differ from patients with recent-onset disease. Handling of intermittently missing observations with last observation carried forward may also represent a limitation of the study; however, only a few observations (<5%) were missing.

In conclusion, the TJC was primarily associated with PROMs and had low associations with the more objective assessments of inflammation, including US scores, and patients with a higher number of tender than swollen joints were found to have lower levels of US synovitis. When patients with predominantly tender joints do not reach CDAS remission, the use of composite scores alone may lead to misinterpretation of disease activity, and thus additional assessments of inflammation may be necessary for these patients. Consequently, taking the high impact of CDAS in the treat-to-target management of RA into account, our results suggest a careful interpretation of CDAS in patients who have predominantly tender joints.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Hammer had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Hammer.

Acquisition of data. Hammer.

Analysis and interpretation of data. Hammer, Michelsen, Provan, Sexton, Lampa, Uhlig, Kvien.

REFERENCES

1. Van der Heijde DM, van 't Hof MA, van Riel PL, Theunisse LA, Lubberts EW, van Leeuwen MA, et al. Judging disease activity in clinical practice in rheumatoid arthritis: first step in the development of a disease activity score. Ann Rheum Dis 1990;49:916–20.
2. Van der Heijde DM, van 't Hof M, van Riel PL, van de Putte LB. Development of a disease activity score based on judgment in clinical practice by rheumatologists. J Rheumatol 1993;20:579–81.
3. Van Gestel AM, Haagsma CJ, van Riel PL. Validation of rheumatoid arthritis improvement criteria that include simplified joint counts. Arthritis Rheum 1998;41:1845–50.
4. Prevoo ML, van 't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight-joint counts: development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum 1995;38:44–8.
5. Aletaha D, Nell VP, Stamm T, Uffmann M, Pflugbeil S, Machold K, et al. Acute phase reactants add little to composite disease activity indices for rheumatoid arthritis: validation of a clinical activity score. Arthritis Res Ther 2005;7:R796–806.
6. Smolen JS, Breedveld FC, Schiff MH, Kalden JR, Emery P, Eberl G, et al. A simplified disease activity index for rheumatoid arthritis for use in clinical practice. Rheumatology (Oxford) 2003;42: 244–57.
7. Felson DT, Smolen JS, Wells G, Zhang B, van Tuyl LH, Funovits J, et al. American College of Rheumatology/European League Against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. Arthritis Rheum 2011;63:573–86.
8. Sokka T, Pincus T. Quantitative joint assessment in rheumatoid arthritis. Clin Exp Rheumatol 2005;23:S58–62.
9. Ossyssek B, Anders S, Grifka J, Straub RH. Surgical synovectomy decreases density of sensory nerve fibers in synovial tissue of non-inflamed controls and rheumatoid arthritis patients. J Orthop Res 2011;29:297–302.
10. Morris VH, Cruwys SC, Kidd BL. Characterisation of capsaicin-induced mechanical hyperalgesia as a marker for altered nociceptive processing in patients with rheumatoid arthritis. Pain 1997;71:179–86.
11. Yunus MB. Editorial review: an update on central sensitivity syndromes and the issues of nosology and psychobiology. Curr Rheumatol Rev 2015;11:70–85.
12. Joharatnam N, McWilliams DF, Wilson D, Wheeler M, Pande I, Walsh DA. A cross-sectional study of pain sensitivity, disease-activity assessment, mental health, and fibromyalgia status in rheumatoid arthritis. Arthritis Res Ther 2015;17:11.
13. Mian AN, Chaabo K, Wajed J, Subesinghe S, Gullick NJ, Kirkham B, et al. Rheumatoid arthritis patients with fibromyalgic clinical features have significantly less synovitis as defined by power Doppler ultrasound. BMC Musculoskelet Disord 2016;17:404.
14. Ranzolin A, Brenol JC, Bredemeier M, Guarienti J, Rizzatti M, Feldman D, et al. Association of concomitant fibromyalgia with worse disease activity score in 28 joints, Health Assessment Questionnaire, and short form 36 scores in patients with rheumatoid arthritis. Arthritis Rheum 2009;61:794–800.
15. Zammurrad S, Munir W, Farooqi A. Disease activity score in rheumatoid arthritis with or without secondary fibromyalgia. J Coll Physicians Surg Pak 2013;23:413–7.
16. Salaffi F, Gerardi MC, Atzeni F, Batticciotto A, Talotta R, Draghessi A, et al. The influence of fibromyalgia on achieving remission in patients with long-standing rheumatoid arthritis. Rheumatol Int 2017;37:2035–42.
17. Pollard LC, Kingsley GH, Choy EH, Scott DL. Fibromyalgic rheumatoid arthritis and disease assessment. Rheumatology (Oxford) 2010;49:924–8.
18. Yunus MB. Role of central sensitization in symptoms beyond muscle pain, and the evaluation of a patient with widespread pain. Best Pract Res Clin Rheumatol 2007;21:481–97.
19. Pollard LC, Ibrahim F, Choy EH, Scott DL. Pain thresholds in rheumatoid arthritis: the effect of tender point counts and disease duration. J Rheumatol 2012;39:28–31.
20. Szkudlarek M, Court-Payen M, Strandberg C, Klarlund M, Klausen T, Østergaard M. Power Doppler ultrasonography for assessment of synovitis in the metacarpophalangeal joints of patients with rheumatoid arthritis: a comparison with dynamic magnetic resonance imaging. Arthritis Rheum 2001;44:2018–23.
21. Naredo E, Bonilla G, Gamero F, Uson J, Carmona L, Laffon A. Assessment of inflammatory activity in rheumatoid arthritis: a comparative study of clinical evaluation with grey scale and power Doppler ultrasonography. Ann Rheum Dis 2005;64:375–81.
22. Keen HI, Wakefield R, Conaghan PG. Optimising ultrasonography in rheumatology. Clin Exp Rheumatol 2014;32 Suppl 85:S–13–6.
23. Navalho M, Resende C, Rodrigues AM, Pereira da Silva JA, Fonseca JE, Campos J, et al. Bilateral evaluation of the hand and wrist in untreated early inflammatory arthritis: a comparative study of ultrasonography and magnetic resonance imaging. J Rheumatol 2013;40:1282–92.
24. Terslev L, Torp-Pedersen S, Savnik A, von der Recke P, Qvistgaard E, Danneskiold-Samsøe B, et al. Doppler ultrasound and magnetic resonance imaging of synovial inflammation of the hand in rheumatoid arthritis: a comparative study. Arthritis Rheum 2003;48: 2434–41.
25. Hammer HB, Bolton-King P, Bakkeheim V, Berg TH, Sundt E, Kongtorp AK, et al. Examination of intra and interrater reliability with a new ultrasonographic reference atlas for scoring of synovitis in patients with rheumatoid arthritis. Ann Rheum Dis 2011;70:1995–8.
26. Villota O, Diaz M, Ceron C, Moller I, Naredo E, Saaibi DL. From a formal training program in musculoskeletal ultrasound (MSUS) to a high reproducibility for Doppler ultrasound in rheumatoid arthritis. Curr Rheumatol Rev 2018;14:264–70.
27. Kristensen LE, Bliddal H, Christensen R, Karlsson JA, Gülfe A, Saxne T, et al. Is swollen to tender joint count ratio a new and useful clinical marker for biologic drug response in rheumatoid arthritis? Results from a Swedish cohort. Arthritis Care Res (Hoboken) 2014;66:173–9.
28. Michelsen B, Kristianslund EK, Hammer HB, Fagerli KM, Lie E, Wierød A, et al. Discordance between tender and swollen joint count as well as patient's and evaluator's global assessment may reduce likelihood of remission in patients with rheumatoid arthritis and psoriatic arthritis: data from the prospective multicentre NOR-DMARD study. Ann Rheum Dis 2017;76:708–11.
29. Smolen JS, Landewé R, Bijlsma J, Burmester B, Chatzidionysiou K, Dougados M, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. Ann Rheum Dis 2017;76:960–77.
30. Hammer HB, Uhlig T, Kvien TK, Lampa J. Pain catastrophizing, subjective outcomes, and inflammatory assessments including

ultrasound: results from a longitudinal study of rheumatoid arthritis patients. Arthritis Care Res (Hoboken) 2018;70:703–12.

31. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315–24.
32. Ziebland S, Fitzpatrick R, Jenkinson C, Mowat A, Mowat A. Comparison of two approaches to measuring change in health status in rheumatoid arthritis: the Health Assessment Questionnaire (HAQ) and modified HAQ. Ann Rheum Dis 1992;51:1202–5.
33. Gossec L, Paternotte S, Aanerud GJ, Balanescu A, Boumpas DT, Carmona L, et al. Finalisation and validation of the rheumatoid arthritis impact of disease score, a patient-derived composite measure of impact of rheumatoid arthritis: a EULAR initiative. Ann Rheum Dis 2011;70:935–42.
34. Rosenstiel AK, Keefe FJ. The use of coping strategies in chronic low back pain patients: relationship to patient characteristics and current adjustment. Pain 1983;17:33–44.
35. Jensen MP, Keefe FJ, Lefebvre JC, Romano JM, Turner JA. One- and two-item measures of pain beliefs and coping strategies. Pain 2003;104:453–69.
36. Tan G, Nguyen Q, Cardin SA, Jensen MP. Validating the use of two-item measures of pain beliefs and coping strategies for a veteran population. J Pain 2006;7:252–60.
37. Hammer HB, Kvien TK, Terslev L. Tenosynovitis in rheumatoid arthritis patients on biologic treatment: involvement and sensitivity to change compared to joint inflammation. Clin Exp Rheumatol 2017;35:959–65.
38. Haavardsholm EA, Aga AB, Olsen IC, Lillegraven S, Hammer HB, Uhlig T, et al. Ultrasound in management of rheumatoid arthritis: ARCTIC randomised controlled strategy trial. BMJ 2016;354:i4205.
39. D'Agostino MA, Boers M, Wakefield RJ, Berner Hammer H, Vittecoq O, Filippou G, et al. Exploring a new ultrasound score as a clinical predictive tool in patients with rheumatoid arthritis starting abatacept: results from the APPRAISE study. RMD Open 2016;2:e000237.
40. Kaeley GS, Nishio MJ, Goyal JR, MacCarter DK, Wells AF, Chen S, et al. Changes in ultrasonographic vascularity upon initiation of adalimumab combination therapy in rheumatoid arthritis patients with an inadequate response to methotrexate. Arthritis Rheumatol 2016;68:2584–92.
41. Van der Ven M, Kuijper TM, Gerards AH, Tchetverikov I, Weel AE, van Zeben J, et al. No clear association between ultrasound remission and health status in rheumatoid arthritis patients in clinical remission. Rheumatology (Oxford) 2017;56:1276–81.
42. Ramírez J, Narváez JA, Ruiz-Esquide V, Hernández-Gañán J, Cuervo A, Inciarte-Mundo J, et al. Clinical and sonographic biomarkers of structural damage progression in RA patients in clinical remission: a prospective study with 12 months follow-up. Semin Arthritis Rheum 2017;47:303–9.

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BRIEF REPORT

Clinical and Structural Efficacy of Hydroxychloroquine in Rheumatoid Arthritis: A Systematic Review

Claire Rempenault,[1] Bernard Combe,[1] Thomas Barnetche,[2] Cécile Gaujoux-Viala,[3] Cédric Lukas,[1] Jacques Morel,[1] and Charlotte Hua[3]

Objective. Hydroxychloroquine (HCQ) improves metabolic and cardiovascular outcomes in patients with rheumatoid arthritis (RA), but its efficacy appears to be moderate as compared to placebo. The aim of our study was to assess the current literature on the clinical and structural efficacy of HCQ in the joints of patients with RA.

Methods. We systematically searched MEDLINE (via PubMed), Embase, Cochrane Library, and the American College of Rheumatology and European League Against Rheumatism annual scientific meeting abstracts for studies available up to November 2017 comparing the efficacy of HCQ in patients with RA, in monotherapy or combined with other conventional synthetic disease-modifying antirheumatic drugs (csDMARDs). Data were extracted by 1 investigator and independently checked by a different investigator.

Results. The literature search revealed 197 articles and abstracts of potential interest, and 11 studies fulfilled inclusion criteria. The clinical and structural efficacy of HCQ was similar to or lower than that for methotrexate or sulfasalazine in monotherapy. HCQ combined with other DMARDs could increase the clinical efficacy.

Conclusion. In addition to its metabolic benefit, combining HCQ with other DMARDs could provide some clinical improvement in patients with RA and inadequate response to previous csDMARDs.

INTRODUCTION

Antimalarials are medicinal agents that have been prescribed for many years, and their potential uses are still being explored. Chloroquine and hydroxychloroquine (HCQ) are weak, basic 4-aminoquinoline compounds. Because of its lower toxicity, HCQ is preferred more than chloroquine in rheumatology practice (1). The mechanism of action of HCQ is thought to be related to interference with lysosomal activity, inhibition of antigen presentation and Toll-like receptor signaling, and dissolution of circulating immune complexes (1). HCQ has been found to improve survival rates in some inflammatory diseases, notably systemic lupus erythematosus, with prevention of lupus flares and protection against irreversible organ damage, thrombosis, and bone mass loss (1). HCQ has also been used for treating rheumatoid arthritis (RA) for several decades, but its overall effect as compared with placebo seems moderate.

Since the emergence of more efficacious disease-modifying antirheumatic drugs (DMARDs), such as methotrexate (MTX) or targeted therapies, HCQ has been less frequently prescribed for RA. However, HCQ could still be a relevant drug for patients with RA, if not for its efficacy in arthritis, at least for its effect on cardiovascular (CV) and metabolic risks. Thus, in a recent systematic literature review and meta-analysis (2), we showed that HCQ may benefit lipid profiles and diabetes mellitus incidence and (to a lesser extent) CV events and insulin resistance in patients with RA. Data on the CV protective role of HCQ are consistent and increasing, but this is not the case for the clinical efficacy of HCQ as treatment for RA. Therefore, the aim of this study was to assess the current literature concerning the clinical and structural efficacy of HCQ in the joints of patients with RA.

MATERIALS AND METHODS

Literature search. We systematically reviewed articles written in English for studies that evaluated the efficacy of HCQ in monotherapy or in combination therapy in RA patients that were published up to November 2017 in MEDLINE (via PubMed),

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No potential conflicts of interest relevant to this article were reported.

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SIGNIFICANCE & INNOVATIONS

- Hydroxychloroquine (HCQ) should not be considered as monotherapy for the majority of patients with early rheumatoid arthritis (RA).
- The combination of HCQ with other conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) could improve some clinical outcomes in RA patients.
- There is a lack of data concerning structural efficacy of HCQ in monotherapy or in combination with other DMARDs in the literature.

Embase, Cochrane Library, and abstracts for the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) annual scientific meetings as early as 2014. Keywords were "rheumatoid arthritis," "Plaquenil," "hydroxychloroquine," and "antimalarial," with no limit on date of publication. In addition, the reference lists of articles were manually searched to identify additional relevant articles. Observational studies and randomized controlled trials (RCTs), but not case reports, were eligible. The trials were initially selected on the basis of their titles and abstracts, then on their full text; duplicates were removed.

Study selection. The population of interest was patients with RA, regardless of disease activity and duration or patient age. We included studies comparing clinical and/or structural efficacy of HCQ, as monotherapy or combined with other conventional synthetic DMARDs (csDMARDs), namely MTX, leflunomide (LEF), or sulfasalazine (SSZ). The selection criteria are shown in Supplementary Table 1 (available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23826/abstract). Study selection was done independently by 2 investigators (CR and CH), and disagreements were resolved by consensus.

Data extraction. Using a predetermined form, 2 investigators (CR and CH) collected data on the study design, sample size, treatments received, patients and control group characteristics (age, sex, disease duration, ongoing DMARDs, prednisone use and dose, exposure time to HCQ and HCQ dose, and response to previous other csDMARDs), definition of the outcome measures, timing and unit of measurements, safety data, and statistical analyses performed. Disagreements were resolved by consensus.

Data synthesis and analysis. Because of the heterogeneity of data, meta-analysis was not feasible. Studies included in the review were classified into 2 categories depending on whether HCQ was evaluated in monotherapy or in combination with other DMARDs.

RESULTS

Literature search results and study characteristics. Initially, 8,428 potentially relevant articles were screened and 8,419 were excluded. Finally, after manually searching reference lists and ACR and EULAR annual meeting abstracts, reports of 11 studies (104,278 patients) were included (Figure 1). Studies' and patients' main characteristics are shown in Tables 1 and 2. Our review focused on comparing HCQ to other csDMARDs.

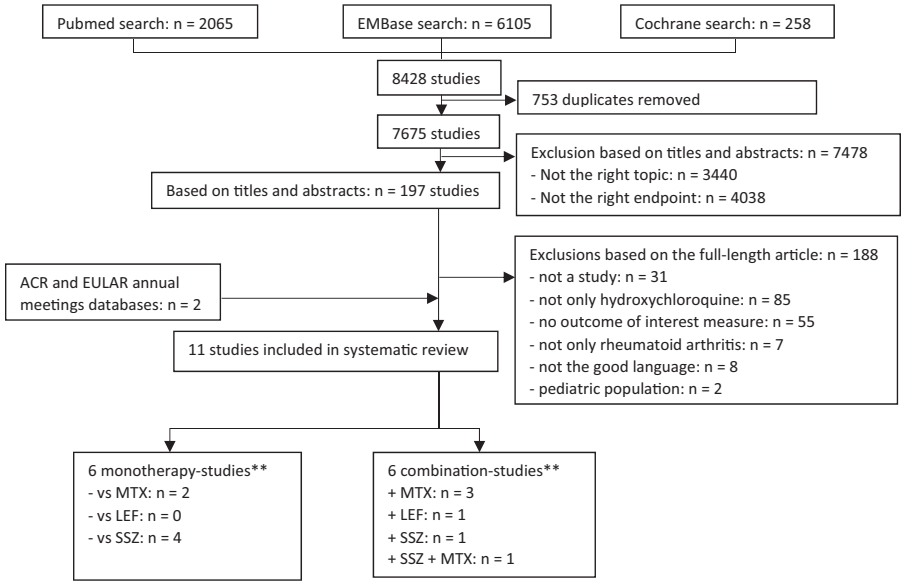

Figure 1. Flow chart of studies in the systematic literature review. *ACR = American College of Rheumatology; EULAR = European League Against Rheumatism; MTX = methotrexate; LEF = leflunomide; SSZ = sulfasalazine. **1 study (6) was included both in the monotherapy part and in the combination part.

Table 1. Characteristics of the patients included in the studies comparing HCQ in monotherapy to other csDMARDs*

Study author, year (ref.)	Type of study	Study duration (wk)	Group (no. patients)	Mean dose	Age (yrs)	Disease duration (yrs)	csDMARD-IR patients, no. (%)
Dixon et al, 1988 (5)	RCT	24	HCQ (13)	400 mg/day	NR	NR	NR
			SSZ (15)	1.5–3 gm/day	NR	NR	NR
Nuver-Zwart et al, 1989 (7)	RCT	48	HCQ (30)	200–400 mg/day	53.0 (22–72)†	1.2 (0.2–13.7)‡	0 (0)
			SSZ (30)	2 gm/day	53.5 (22–75)†	0.9 (0.2–10)‡	0 (0)
Van der Heijde et al, 1989 (8)	RCT	48	HCQ (28)	200–400 mg/day	53.1 (22–72)†	1.3	0 (0)
			SSZ (22)	2 gm/day	53.5 (22–75)†	1.1	0 (0)
Faarvang et al, 1993 (6)	RCT	24	HCQ (31)	250 mg/day	NR	6.3 (0–37)‡	NR
			SSZ (29)	2 gm/day	NR	6.3 (0–37)‡	NR
Alam et al, 2012 (3)	RCT	24	HCQ (30)	200–400 mg/day	42.9 ± 9.2§	1.8 ± 0.3§	0 (0)
			MTX (30)	7.5–17.5 mg/wk	41.7 ± 12.2§	2.3 ± 0.4§	0 (0)
Gossen et al, 2016 (4)	Cohort	260	HCQ (16,796)	NR	57.8 ± 15.0§	NR	NR
			MTX (85,082)	NR	57.8 ± 15.0§	NR	NR

* HCQ = hydroxychloroquine; csDMARDs = conventional synthetic disease-modifying antirheumatic drugs; ref. = reference; IR = inadequate response; RCT = randomized controlled trial; SSZ = sulfasalazine; NR = not reported; MTX = methotrexate.
† Values are the years of age (minimum–maximum range).
‡ Values are the years of disease duration (minimum–maximum range).
§ Values are the mean ± SD.

Efficacy of HCQ monotherapy. Most patients included in the studies that evaluated HCQ as monotherapy had early RA (disease duration of <5 years). They were also naive to csDMARDs (Table 1).

Efficacy versus MTX. Only 2 studies evaluated MTX (3,4). In an open-label controlled clinical trial (3) comparing MTX versus HCQ, disease activity (based on Disease Activity Score in 28 joints [DAS28]) decreased significantly in both groups after 6 months of treatment, but the clinical response was significantly better in the MTX group ($P < 0.001$). There was no difference in the incidence of adverse events between the 2 groups. In a second study (4), receipt of biologics was less frequent for patients receiving HCQ during the 5 years of follow-up as compared with those receiving MTX (hazard ratio 0.283 [95% confidence interval 0.25–0.31], $P < 0.0001$). Of note, this last study was a cohort study, without randomization, and it is likely that patients receiving HCQ had less severe disease, with consequently fewer need for biologics than those receiving MTX. No study assessed structural efficacy of HCQ compared with MTX.

Efficacy versus SSZ and versus LEF. Four studies that evaluated SSZ were included (5–8). In an open-label study (5) and 2 double-blind RCTs (6,7), the efficacy of HCQ and SSZ was similar for erythrocyte sedimentation rate (ESR), morning stiffness, swollen joint count, joint pain, patient or physician global assessment at 6 months, and mean change in articular index between week 0 and week 24. Safety was evaluated in 2 studies (6,7) and was similar between SSZ and HCQ. Two studies assessed the structural efficacy of HCQ compared to SSZ. In a double-blind RCT (8), radiographic progression rates at 48 weeks were significantly higher with HCQ than SSZ ($P < 0.02$); whereas another double-blind RCT (9) found slight progressions of the lesions specific to RA on the hands and the wrists of patients in the HCQ

Table 2. Characteristics of the patients included in the studies comparing HCQ in combination to other csDMARDs*

Study author, year (ref.)	Study type	Study duration (wks)	Group (no. patients)	Mean dose	Age, years	Disease duration, years	csDMARD-IR patients, no. (%)
Faarvang et al, 1993 (6)	RCT	24	HCQ (31)	250 mg/day	NR	6.3 (0–37)†	NR
			SSZ + HCQ (31)	2 gm/day + 250 mg/day	NR	NR	NR
O'Dell et al, 2002 (13)	RCT	104	MTX + SSZ + HCQ (58)	12.5–17.5 mg/wk + 2 g/day + 400 mg/day	48.9 (26–66)‡	6.9 ± 6.8§	31 (53.4)
			MTX + SSZ (55)	12.5–17.5 mg/wk + 2 gm/day	52.5 (25–71)‡	5.8 ± 5.9§	28 (50.9)
Weaver et al, 2006 (9)	Cohort	52	MTX + HCQ (325)	12.5 mg/wk + 400 mg/day	53.8 ± 14.5§	4.6 ± 6.9§	303 (93.2)
			MTX (941)	12.5 mg/wk	56.8 ± 14.0§	3.5 ± 7.1§	866 (92.0)
Dissanayake et al, 2014 (10)	RCT	52	MTX + HCQ (39)	20–25 mg/wk + 400 mg/day	NR	NR	NR
			MTX (35)	20–25 mg/wk	NR	NR	NR
Li et al, 2016 (12)	RCT	48	LEF + HCQ (89)	10–20 mg/day + 400 mg/day	48.7 ± 12.9§	6.1 ± 7.3§	NR
			LEF (87)	10–20 mg/day	48.7 ± 12.9§	6.1 ± 7.3§	NR
Brunekreef and Moens, 2017 (11)	Cohort	104	MTX (297)	NR	NR	NR	NR
			MTX + HCQ (156)	NR	NR	NR	NR

* HCQ = hydroxychloroquine; csDMARDs = conventional synthetic disease-modifying antirheumatic drugs; ref. = reference; IR = inadequate response; RCT = randomized controlled trial; SSZ = sulfasalazine; NR = not reported; MTX = methotrexate; LEF = leflunomide.
† Values are the years of disease duration (minimum–maximum range).
‡ Values are the years of age (minimum–maximum range).
§ Values are the mean ± SD.

and the SSZ groups without statistically significant difference among the 2 groups. No study comparing LEF was retrieved.

Efficacy of HCQ combined with other csDMARDs. Most patients included in the studies that evaluated HCQ in combination had established RA (disease duration >5 years) and showed insufficient response to csDMARDs (Table 2).

Efficacy of HCQ + MTX versus MTX. Three studies were included (9–11). In 1 study of data from an observational registry (9), the odds of achieving a modified ACR criteria for 20% improvement in disease activity (ACR20) response rate at 12 months did not differ between the 2 groups. The proportion of adverse events was 4% in the MTX group versus 11% in the MTX + HCQ group (no statistical comparison was performed and no precision of the type of adverse events was provided). In 1 open-label study presented as an abstract at the ACR 2014 annual meeting (10) and in a cohort study presented as an abstract at the EULAR 2017 annual meeting (11), adding HCQ to MTX had some interest. In the first trial (10), DAS28 scores improved in both early-RA patient groups, but improvement was significantly better with MTX + HCQ than MTX at 3 months (–2.2 versus –1.3; $P = 0.003$) and 12 months (–2.9 versus –1.9; $P = 0.047$). In the second trial (11), remission within 12 months was more frequent with combination treatment (MTX + HCQ + triamcinolone) than with MTX alone (88.2% versus 72.2%). No study assessed the structural efficacy of HCQ + MTX with MTX alone.

Efficacy of HCQ + SSZ versus SSZ. One multicenter, double-blind RCT found no statistically significant difference between combination treatment and SSZ monotherapy for ESR, morning stiffness, swollen joint count, joint pain, or patient or physician global assessment at 6 months (6) and structural progression. The safety profile did not differ between the 2 groups.

Efficacy of HCQ + LEF versus LEF. One single-blind RCT compared HCQ + LEF to LEF as step-down maintenance treatment after obtaining clinical remission or low disease activity with MTX + LEF + HCQ (12). By 48 weeks, the 2 groups did not differ in disease activity or maintenance rate ($P = 0.53$). Adverse events were mild to moderate without separate data for each group. No study assessed structural efficacy of HCQ + LEF compared with LEF monotherapy.

Efficacy of HCQ + MTX + SSZ versus MTX + SSZ. We included only 1 double-blind RCT comparing MTX + SSZ + HCQ to MTX + SSZ (13). ACR20 and ACR50 response rates were higher with triple therapy than with MTX + SSZ without HCQ (78% versus 49%; $P = 0.02$, and 55% versus 29%; $P = 0.005$, respectively) at 2 years. A subgroup analysis retained the superiority of triple therapy over MTX + SSZ in terms of ACR20 ($P < 0.01$) and ACR50 response ($P = 0.02$) at 2 years in patients with insufficient response to MTX but not those who were MTX naive. Adverse events were infrequent and evenly distributed between the 2 groups. No study assessed structural efficacy of HCQ + MTX + SSZ compared with MTX + SSZ.

DISCUSSION

According to this systematic literature review, HCQ should not be considered as monotherapy for the majority of patients with early RA but might provide moderate clinical benefit to RA patients in terms of disease activity control when used in combination with other csDMARDs. One explanation for the potential efficacy of HCQ combined with other csDMARDs is that HCQ might increase exposure to other csDMARDs and so increase their efficacy (2). The benefit in efficiency with the combination of csDMARDs is currently recognized in international guidelines, which consider the use in patients with insufficient response to MTX in the absence of poor prognostic factors (14).

The aim of this systematic literature review was to assess the clinical and structural efficacy of HCQ and not to evaluate the safety of HCQ. However, we have reported safety data when available. Due to the number of included patients in the selected trials, it's difficult to extrapolate firm conclusions on the safety profile of HCQ when used as monotherapy or in combination in patients with RA. However, according to these data, HCQ seemed to have a similar safety profile compared to other csDMARDs, which is not surprising since HCQ is considered to be a safe and well-tolerated drug in some other rheumatic diseases, namely lupus (1). In addition, adverse events did not seem to be increased when adding HCQ to other csDMARDs. In this respect, a recent study has shown that low persistence rates of triple therapy (MTX + SSZ + HCQ) that were observed in RA patients were mainly attributed to adverse drug events due to SSZ and not to HCQ (15).

Our systematic literature review has several limitations. Data were scarce and publication dates were mostly before the 2000s. Treatment dosages differed among studies and often did not correspond to our current practice, especially for MTX, which was often underdosed. Not all of the included studies were randomized, and in nonrandomized trials HCQ was likely prescribed to patients with less severe RA, which may account for the better outcomes of these patients versus patients receiving other csDMARDs. Furthermore, apart from 2 studies (6,8), no study evaluated HCQ structural efficacy.

In conclusion, treatment dosages, main outcomes, and study results were too heterogeneous in this systematic literature review to formally conclude on the efficacy of HCQ in RA. When used in monotherapy, HCQ clinical and structural efficacy seemed to be similar to or lower than that of MTX or SSZ. However, most studies suggested that HCQ could slightly improve various outcome measures of disease activity when combined with other csDMARDs, at least in patients with established RA and insufficient response to csDMARDs. Consequently, HCQ could be used in combination with other

csDMARDs for some patients with RA. The known metabolic and protective CV effects of HCQ and its low cost and good safety profile are arguments strengthening this hypothesis. Obviously, recent and well-conducted studies are warranted to support this conclusion.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Rempenault had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Rempenault, Combe, Barnetche, Gaujoux-Viala, Lukas, Morel, Hua.

Acquisition of data. Rempenault, Hua.

Analysis and interpretation of data. Rempenault, Combe, Barnetche, Hua.

REFERENCES

1. Wallace DJ, Gudsoorkar VS, Weisman MH, Venuturupalli SR. New insights into mechanisms of therapeutic effects of antimalarial agents in SLE. Nat Rev Rheumatol 2012;8:522–33.
2. Rempenault C, Combe B, Barnetche T, Gaujoux-Viala C, Lukas C, Morel J, et al. Metabolic and cardiovascular benefits of hydroxychloroquine in patients with rheumatoid arthritis: a systematic review and meta-analysis. Ann Rheum Dis 2018;77:98–103.
3. Alam MK, Sutradhar SR, Pandit H, Ahmed S, Bhattacharjee M, Miah AH, et al. Comparative study on methotrexate and hydroxychloroquine in the treatment of rheumatoid arthritis. Mymensingh Med J 2012;21:391–8.
4. Gossen N, Jacob L, Kostev K. Second-line therapy with biological drugs in rheumatoid arthritis patients in German rheumatologist practices: a retrospective database analysis. Rheumatol Int 2016;36:1113–8.
5. Dixon JS, Greenwood M, Bird HA. How reliable is ESR as a measure of disease activity in rheumatoid arthritis treated with hydroxychloroquine? Clin Rheumatol 1988;7:262–6.
6. Faarvang KL, Egsmose C, Kryger P, Pødenphant J, Ingeman-Nielsen M, Hansen TM. Hydroxychloroquine and sulphasalazine alone and in combination in rheumatoid arthritis: a randomised double blind trial. Ann Rheum Dis 1993;52:711–5.
7. Nuver-Zwart IH, van Riel PL, van de Putte LB, Gribnau FW. A double blind comparative study of sulphasalazine and hydroxychloroquine in rheumatoid arthritis: evidence of an earlier effect of sulphasalazine. Ann Rheum Dis 1989;48:389–95.
8. Van der Heijde DM, van Riel PL, Nuver-Zwart IH, Gribnau FW, vad de Putte LB. Effects of hydroxychloroquine and sulphasalazine on progression of joint damage in rheumatoid arthritis. Lancet 1989;1:1036–8.
9. Weaver AL, Lautzenheiser RL, Schiff MH, Gibofsky A, Perruquet JL, Luetkemeyer J, et al. Real-world effectiveness of select biologic and DMARD monotherapy and combination therapy in the treatment of rheumatoid arthritis: results from the RADIUS observational registry. Curr Med Res Opin 2006;22:185–98.
10. Dissanayake T, Martin L, Barr S, Pennecy C, Morris G, Mosher D. Efficacy of methotrexate monotherapy compared to combination therapy with methotrexate and hydroxychloroquine in the treatment of early rheumatoid arthritis after 12 months of treatment. J Rheumatol 2014;41:1493–4.
11. Brunekreef T, Moens HB. Remission induction with methotrexate step-up therapy versus combination of hydroxychloroquine, methotrexate and triamcinolone: 3 year results. Ann Rheum Dis 2017;76 Suppl 2:147–8.
12. Li R, Zhao JX, Su Y, He J, Chen LN, Gu F, et al. High remission and low relapse with prolonged intensive DMARD therapy in rheumatoid arthritis (PRINT): a multicenter randomized clinical trial. Medicine (Baltimore) 2016;95:e3968.
13. O'Dell JR, Leff R, Paulsen G, Haire C, Mallek J, Eckhoff PJ, et al. Treatment of rheumatoid arthritis with methotrexate and hydroxychloroquine, methotrexate and sulfasalazine, or a combination of the three medications: results of a two-year, randomized, double-blind, placebo-controlled trial. Arthritis Rheum 2002;46:1164–70.
14. Smolen JS, Landewé R, Bijlsma J, Burmester G, Chatzidionysiou K, Dougados M, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. Ann Rheum Dis 2017;76:960–77.
15. Erhardt DP, Cannon GW, Teng CC, Mikuls TR, Curtis JR, Sauer BC. Low persistence rates in patients with rheumatoid arthritis treated with triple therapy and adverse drug events associated with sulfasalazine. Arthritis Care Res (Hoboken) 2019;71:1326–35.

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Systematic Review of the Impact of Inflammatory Arthritis on Intimate Relationships and Sexual Function

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Objective. To systematically review evidence of the impact of inflammatory arthritis on, or association of inflammatory arthritis with, intimate relationships and sexual function.

Methods. Ovid Medline, Ovid PsycINFO, Ovid Embase, and EBSCO CINAHL databases were searched. Two independent reviewers selected articles, extracted data, and conducted manual searches of reference lists from included studies and previous reviews. The quality of evidence was assessed using standard risk-of-bias tools.

Results. Fifty-five eligible studies were reviewed. Of these, 49 (89%) were quantitative, 5 (9.1%) were qualitative, and 1 (1.8%) used a mixed-method design. Few quantitative studies were rated as low risk of bias (n = 7 [14%]), many were rated as moderate (n = 37 [74%]) or high risk (n = 6 [12%]). Quantitative study sample sizes ranged from 10 to 1,272 participants, with a reported age range 32–63 years. Qualitative study sample sizes ranged from 8 to 57 participants, with a reported age range 20–69 years. In studies reporting the Female Sexual Function Index, all inflammatory arthritis groups demonstrated mean scores ≤26.55 (range of mean ± SD scores: 14.2 ± 7.8 to 25.7 ± 4.7), indicating sexual dysfunction. In studies reporting the International Index of Erectile Function, all inflammatory arthritis groups reported mean scores ≤25 (range of mean ± SD scores: 16.0 ± 5.3 to 23.8 ± 7.0), indicating erectile dysfunction. Key qualitative themes were impaired sexual function and compromised intimate relationships; prominent subthemes included inflammatory arthritis–related pain and fatigue, erectile dysfunction, diminished sexual desire, and sexual function fluctuations according to disease activity.

Conclusion. Sexual dysfunction appears highly prevalent among men and women with inflammatory arthritis, and increased clinician awareness of this impairment may guide provision of tailored education and support.

INTRODUCTION

The International Classification of Functioning, Disability and Health considers sexual health as comprising 2 distinct constructs: "sexual function," relating to body functions, and "intimate relationships," relating to activity and participation (1). Sexual function in individuals with inflammatory arthritis may be affected by disease activity (pain, functional limitations, and fatigue), psychological distress related to the disease, including reduced self-esteem and altered body image perception, and/or side effects from pharmacologic treatments (fatigue, lowered mood, vaginal dryness, and erectile dysfunction) (2–10). Intimate relationships may, in turn, be affected by these and other factors (11,12), potentially contributing to relationship dissatisfaction and family breakdown (2,13–15). The impact of inflammatory arthritis on sexual health appears to be an issue worldwide, because it has been identified in populations in Europe, America, Asia, and Africa (13,16–19).

Sexual health and family planning are important considerations not only for individuals living with inflammatory arthritis but also for the health practitioners who treat them (20), yet these issues are rarely comprehensively addressed in clinical practice (4,8,9,16,18,19,21–24). Earlier research has shown that 36–70% of individuals with rheumatoid arthritis (RA) experience impaired sexual health associated with their disease

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SIGNIFICANCE & INNOVATIONS

- To our knowledge, this is the first systematic review to consider the impact of all types of inflammatory arthritis on intimate relationships and sexual function in both sexes based on evidence from qualitative and quantitative studies.
- Eligible studies were primarily quantitative in design and showed a higher prevalence of sexual dysfunction among the inflammatory arthritis populations in comparison to healthy populations; however, the impact on intimate relationships was rarely explored.
- Qualitative studies revealed that sexual dysfunction was impaired in inflammatory arthritis due to pain, reduced sexual desire, erectile dysfunction, and fatigue, along with the same stressors that affect the general population, such as stress and other concerns.

(5,7,13,16,19,21,22,25,26), but the majority have not discussed this problem with a health professional (27). Additionally, individuals with inflammatory arthritis vary in their preference of health professional with whom to discuss these issues (27), suggesting all health professionals involved in an individual's care should gain an improved understanding of the potential impacts of inflammatory arthritis on sexual function and intimate relationships.

The impact of inflammatory arthritis on sexual health has been investigated previously, but systematic reviews published to date have important limitations (5,6,28,29). First, many have not assessed the impact of inflammatory arthritis on both sexes, because most have focused on female sexual function only (29–39). Second, most reviews have been disease-specific (6,28–34,36–51), limiting transferability of the findings to other inflammatory arthritis conditions. Although some reviews have considered rheumatic conditions more broadly (10,35,52,53), they do not include contemporary evidence (3,10,21,22,54–100). Finally, earlier reviews have largely been restricted to Western populations (6,28).

To overcome existing limitations, we aimed to undertake a systematic review of self-reported perceptions (concerns, thoughts, beliefs, and opinions) concerning the impact of inflammatory arthritis on, or the association of inflammatory arthritis with, intimate relationships and sexual function among individuals with inflammatory arthritis.

MATERIALS AND METHODS

Study design. A systematic review of quantitative and qualitative studies was undertaken in 2018. The systematic review protocol was registered on PROSPERO International Prospective Register of Systematic Reviews (registration number CRD42017074189). The review is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement (see Supplementary Table 1, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23857/abstract).

Eligibility for inclusion. Primary qualitative, quantitative, and mixed-method design studies published in English in peer-reviewed journals were included. Relevant self-reported outcomes included concerns, thoughts, beliefs, and opinions of individuals with inflammatory arthritis, concerning the impact of their inflammatory arthritis on, or the association of inflammatory arthritis with, intimate relationships and sexual function and were drawn from quantitative studies (e.g., surveys) or qualitative studies (e.g., interviews, focus groups). Studies conducted in any care setting were included. Studies that included males or females with a diagnosis of inflammatory arthritis (including but not limited to RA, seronegative arthritis, systemic lupus erythematous (SLE), systemic scleroderma/systemic sclerosis (SSc), ankylosing spondylitis (AS), psoriatic arthritis, connective tissue disease, vasculitis, Sjögren's syndrome (SS), spondyloarthritis, autoimmune arthritis, and juvenile idiopathic arthritis were included. Patients aged ≥16 years were eligible for the inclusion. Studies where the outcomes were not directly reported by individuals who live with inflammatory arthritis (e.g., where outcomes were only reported by spouses) were excluded. Abstracts and conference proceedings were also excluded.

Search strategy and selection of studies. Four electronic databases (Ovid Medline, Ovid PsycINFO, Ovid Embase, and EBSCO CINAHL Plus) were searched systematically from January 1, 1990 to May 8, 2018. An initial search for studies was conducted in Medline and Embase, and an analysis of text words and subject terms was then used by one reviewer (LR) to develop the search. Subject classification systems for each database were also investigated (with input from INA, SVD, and AMB). The final searches of all 4 electronic databases was executed by 1 reviewer (LR) using the appropriate specifications of each database. The comprehensive search strategy used for each of the 4 databases is shown in the Supplementary materials, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23857/abstract. Gray literature was not considered. Two reviewers (LJR and SRD) independently screened the titles and abstracts of the yield to determine each article's eligibility for inclusion. Any discordance regarding eligibility was discussed and resolved through consensus, with arbitration by a third reviewer (AMB), if required. The full texts of the potentially eligible articles were reviewed independently by 2 reviewers (LJR and SRD) to confirm eligibility. Any discordance in selection of full texts was resolved through consensus and arbitrated by a third reviewer (AMB), if required. The reference

lists of all included full-text studies and any systematic reviews identified were manually screened by the reviewers (LJR and SRD). Citation screening and selection were documented and summarized in a PRISMA-compliant flow chart (Figure 1).

Data extraction. Data extraction was undertaken by 2 reviewers independently (LJR and SRD) and a consensus data set derived. A standardized data extraction template was developed using Microsoft Excel and piloted on 3 eligible articles by LJR, SRD, INA, SVD, and AMB. Data from quantitative and qualitative studies were extracted separately. The following data were extracted (where available) for each study: research question, study design, study population including diagnoses, geographic region, study setting, demographic characteristics (e.g., age, sex), primary and secondary outcome measures, and results. For qualitative studies, the first-order data (the quotes from the primary study participants) and the second-order data (themes and subthemes developed by authors of included articles) were extracted to preserve the links to the original quotes and the context from the primary study.

Quality and risk-of-bias appraisal. The methodologic quality of the included studies was appraised independently by 2 reviewers (LJR and SRD) and a consensus appraisal score was derived. Quantitative studies were appraised using the Hoy et al risk-of-bias tool (101), while the Critical Appraisal Skills Program (CASP) tool was used for qualitative studies (102). While there are several risk-of-bias assessment tools available for quantitative and qualitative studies, these tools were selected for ease of use and alignment with other patient-centered systematic reviews relevant to rheumatic diseases (103–108). The tools were piloted on 3 eligible articles to ensure interrater consistency. Any discordance regarding critical appraisal was discussed and resolved through consensus, with arbitration by a third reviewer (AMB), if required.

Data analysis and synthesis of results. Two reviewers (LJR and SRD) independently extracted and synthesized the data from the eligible studies. Descriptive and outcome data from quantitative studies were summarized and reported descriptively. The independent data sets relating to the quantitative studies were compared for consistencies, with any discrepancies resolved to create a composite data set. The results of the qualitative studies were metasynthesized using a staged approach of thematic analysis (109–111). Independent data files were merged and compared, with discrepancies resolved by consensus, and if necessary, by arbitration with AMB. First, each reviewer read the full-text article multiple times, highlighting relevant sections that related to the review to inductively develop initial categories or themes. These themes/categories were organized into an initial thematic framework, which was reviewed by other authors (INA, SVD, and AMB) to consider construct validity and clinical meaningfulness. Second, the framework was populated with extracted data from the studies to ensure the inductively derived themes and subthemes were

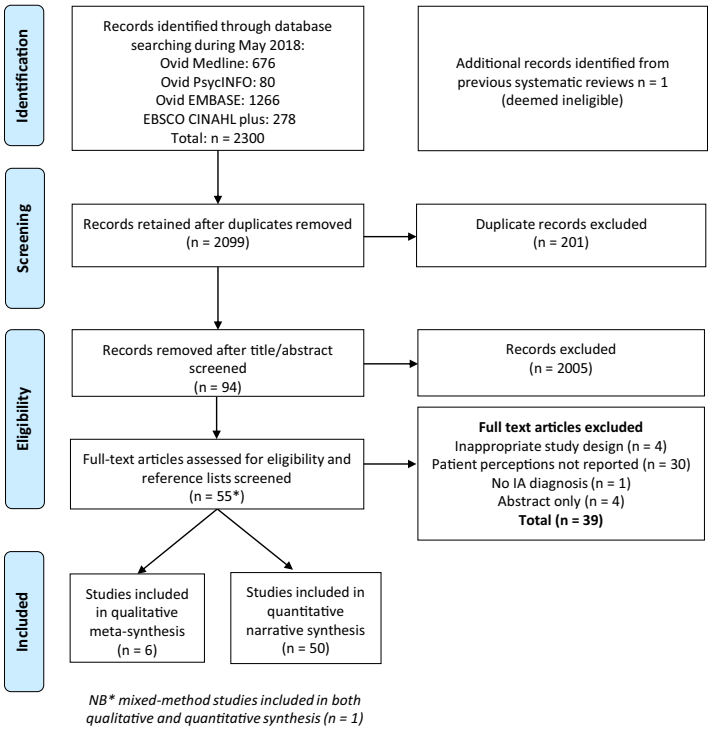

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analysis flowchart of included studies. IA = inflammatory arthritis.

underpinned by primary data. Once populated, the framework was again revised and reviewed by the authors.

Assessment of confidence profile. The GRADE–Confidence in the Evidence from Reviews of Qualitative research (GRADE-CERQual) method was used to assess confidence in the metasynthesis findings across 4 domains: methodologic limitations, coherence, adequacy of data, and relevance of all the individual primary research study findings contributing to the metasynthesis (112), with each domain assigned a level of concern (minor, moderate, substantial). The review team (LJR, SRD, AMB) evaluated the confidence profile through discussions and allocated an overall level of confidence (high, moderate, low, or very low) to each finding in the metasynthesis.

RESULTS

Search results and description of included studies. The search strategy returned 2,100 unique citations, of which 55 (2.6%) (7–9,19,21,22,27,58–100,113–117) met the inclusion criteria (Figure 1). Descriptive characteristics of the 55 included studies are summarized in Table 1. Of the included studies, 49 (89.1%) were quantitative (7,9,19,21,22,27,58–74,76,77,79,80,82–86,88–92,94–100,113–117), 5 (9.1%) were qualitative (75,78,81,87,93), and 1 (1.8%) used a mixed-method design (8). Four of the qualitative studies used focus groups or semistructured interviews (78,81,87,93), while all the quantitative studies used patient-reported questionnaires (7,9,19,21,22,27,58–74,76,77,79,80,82–86,88–92,94–100,113–117).

Included studies were conducted in the following countries where reported (n = 45): the European Union (n = 7 [37.8%]) (8,19,27,60,67,70,77,81,85,87,88,92–96,115), Middle East (n = 14 [31.1%]) (22,63,65,66,69,73,75,76,78,82,84,89,98,117), North America (n = 5 [11.1%]) (58,61,95,113,114), Africa (n = 4 [8.9%]) (7,74,83,86), Oceania (n = 1 [2.2%]) (68) Asia (n = 2 [4.4%]) (79,97), and South America (n = 2 [4.4%]) (64,90). Controlled cohort study designs were adopted by 34 of the quantitative studies (69.4%) (9,19,22,58,59,62–67,69,70,73,76,79,80,82–85,89,90,94–100,113,116,117), while 16 (32.7%) used single group designs (7,21,27,60,61,68,71,72,74,77,86,88,91,92,114,115). Sixteen studies (29.1%) involved individuals with RA only (7,8,19,27,66,73,76,80–83,86,88,91,92,94,98), 16 (29.1%) with AS only (21,22,59,60,62–65,69–71,78,79,90,116,117), 10 (18.2%) with SSc only (61,67,74,75,77,88,95,96,113,115), 5 (9.1%) with SLE only (58,68,87,97,114), 4 (7.3%) with SS only (85,89,99,100), and 4 (7.3%) with mixed inflammatory arthritis conditions (9,72,84,93). Mean ± SD inflammatory arthritis disease duration ranged from 3.3 ± 2.6 to 19.0 ± 11.6 years, and 52 studies (94.5%) reported that participants had a disease duration of >5 years (8,19,21,22,27,60,62,64–69,70–72,74–81,83,84,86–98,100,113,115–117).

Participants were recruited from tertiary hospital outpatient rheumatology clinics in 11 studies (20%) (9,19,60,65,66,68,77,79,82,91,93), research hospital outpatient rheumatology clinics in 2 studies (3.6%) (76,98), nontertiary outpatient rheumatology clinics in 13 studies (23.6%) (7,8,19,27,67,70,72,81,87,88,97,100,113), university hospitals in 18 studies (32.7%) (19,22,61,63,64,69,73–75,78,81,83,85,86,89,90,96,117), from research or disease databases/registries in 6 studies (10.9%) (58,92,94,95,114,115), and in 8 studies (14.5%) the setting was not stated (21,59,62,71,80,84,99,116). Sample size ranged from 10 to 1,272 participants (reported age range 32–63 years; proportion female 0–100%) in quantitative studies (7,9,19,21,22,27,58–74,76,77,79,80,82–86,88–92,94–100,113–117) and from 8 to 57 participants (reported age range 20–69 years; proportion female 0–53%) in qualitative and mixed-method studies (8,75,78,81,87,93).

Outcomes reported. Outcomes from quantitative studies highlighted the fact that sexual dysfunction was more prevalent among individuals with inflammatory arthritis for both men and women compared with controls (118) (Table 2). The 2 most common instruments employed were the Female Sexual Function Index (FSFI) and the International Index for Erectile Function (IIEF).

FSFI scores were reported in 20 studies (36.4%) (Figure 2). All patient groups demonstrated a mean score lower than the FSFI threshold for sexual dysfunction of ≤26.55 (119), indicating the presence of sexual dysfunction (7,22,61,66,67,69,70,73,74,77,80,84,85,86,88,89,96,97,99,100). Of these 20 studies, 15 (75%) compared an inflammatory arthritis patient group with a control group, highlighting the fact that most of the inflammatory arthritis groups had lower FSFI mean scores than controls (22,61,66,67,69,70,73,80,84,85,89,96,97,99,100). In 2 studies (20%), control groups demonstrated greater sexual dysfunction than the inflammatory arthritis patient groups (69,80). In 5 studies (25%), control groups reported sexual dysfunction, based on the FSFI threshold, although their mean scores were still higher than inflammatory arthritis patient groups (66,67,69,80,99). Five studies (25%) did not use control groups, but the mean scores reported for their inflammatory arthritis groups on the FSFI appeared much lower than the mean scores of studies with control groups (7,74,77,86,88). Comparing outcomes by disease, populations with SSc reported mean FSFI scores that tended to be the lowest (61,67,74,77,89,96), although some studies were uncontrolled (74,77).

Seven studies (12.7%) used the IIEF to assess the impact of inflammatory arthritis on men's erectile function (62,65,79,88,90,116,117) (Figure 3). In all studies (62,65,73,79,88,90,116,117), the mean IIEF scores were ≤25, indicating erectile dysfunction (120). All but 1 study compared IIEF scores of inflammatory arthritis patients to controls and showed lower mean scores in the inflammatory arthritis group (62,65,79,90,116,117). Mean scores for most control groups suggested normal erectile function except for 2 studies, where the control group mean scores were on the threshold for erectile dysfunction, but these scores were not lower than the inflammatory arthritis patients'

Table 1. Summary of included studies*

Study	Country	Design	Setting	IA group, no., sex (%), age mean ± SD years	Type of IA, no. (%)	Disease duration†	Control group, no., sex (% when given), age mean ± SD years
Abda et al, 2016 (83)	Egypt	Quantitative cross-sectional controlled cohort survey	Department of rheumatology and rehabilitation, university hospital	200, female (100), 44.2 ± 9.1	RA: 200	5.8 ± 4.1	100, female, 42.5 ± 6.3
Aguiar et al, 2014 (72)	Not stated	Quantitative cross sectional single group survey	Outpatient rheumatology clinic in private hospital setting	76, female (50), 46.1 ± 12.1	PsA: 31 (41); AS: 30 (39); undifferentiated SpA: 9 (12); IBD: 6 (8)	12.2 ± 10.3	NA
Akkurt et al, 2016 (84)	Turkey	Quantitative cross-sectional controlled cohort survey	Not stated	54, female (100), 39.3 ± 8.6	IA: 100	8.5 ± 5.1	56, female, 37.6 ± 9.6
Aras et al, 2013 (66)	Turkey	Quantitative cross-sectional controlled cohort survey	Department of physical medicine and rehabilitation in a tertiary hospital setting	104, female (100), 48.6 ± 8.6	RA: 104	9.3 (SD not reported)	82, female, 46.7 ± 7.6
Bagcivan et al, 2015 (78)	Turkey	Qualitative study (semistructured interviews)	Rheumatology outpatient clinic, university hospital	23, female (30), 29.6 ± 6.0	AS: 23	5.4 ± 3.5	NA
Bal et al, 2011 (62)	Not stated	Quantitative cross-sectional controlled cohort survey	Not stated	37, male (100), 42.8 ± 10.8	AS: 37	10 ± 9	67, male, 43.6 ± 5.9
Bhadauria et al, 1995 (113)	US	Quantitative cross-sectional controlled cohort survey	Private practice of rheumatologist in private hospital setting	60, female (100), 50.5 ± 12.0	SSc: 60	10.9 ± 7.6	23, female, 46.0 ± 12.3
Bongi et al, 2013 (67)	Italy	Quantitative cross-sectional controlled cohort survey	Outpatient clinic and day hospital for the division of rheumatology	46, female (100), 56.1 ± 12.4	SSc: 46	10 ± 6	46, female, 52.0 ± 9.0
Coskun et al, 2014 (73)	Turkey	Quantitative cross-sectional controlled cohort survey	Outpatient department of rheumatology clinic, Uludag University Hospital	32, female (100), 38.4 ± 6.9	RA: 32	Not stated	20, female, 39.3 ± 5.5
Daleboudt et al, 2013 (68)	New Zealand	Quantitative cross-sectional single group survey	Outpatient clinic, city hospital	106, female (94.3), 43.3 ± 14.9	SLE: 106	10.2 ± 9.1	NA
Demir et al, 2013 (69)	Turkey	Quantitative cross-sectional controlled cohort survey	Outpatient rheumatology clinic, Bezmialem Vakif University	2, female (100), 39.3 ± 6.3, 23 patients with AS	AS: 23	3.3 ± 2.6	27, female, 37.6 ± 9.6
Dhakad et al, 2015 (79)	India	Quantitative longitudinal controlled cohort survey	Rheumatology department of a tertiary hospital with data collected at baseline	100, male (100), 32.4 ± 9.8	AS: 100	5.1 ± 0.1	100, male, 30.1 ± 6.2
Dincer et al, 2007 (59)	Not stated	Quantitative cross-sectional controlled cohort survey	Not stated	68, male (100), 32.9 ± 11.0	AS: 68	Not stated	45, male, 30.1 ± 6.24

(Continued)

Table 1. (*Cont'd*)

Study	Country	Design	Setting	IA group, no., sex (%), age mean ± SD years	Type of IA, no. (%)	Disease duration†	Control group, no., sex (% when given), age mean ± SD years
Dorner et al, 2018 (91)	Not stated	Quantitative cross-sectional single group survey	Outpatient clinic of a nontertiary hospital	54, female (61), 47.8 ± 10.6	RA: 54	Median (IQR) 5 (2–8)	NA
Druley et al, 1997 (114)	US	Quantitative cross-sectional single group survey	Chapters of the Lupus Foundation of America, community setting	74, female (100), 42.8 ± 12.9	SLE: 74	Not stated	NA
El Miedany et al, 2012 (7)	Egypt	Quantitative cross-sectional single group survey	Rheumatology outpatient clinic in private hospital setting	231, female (44.7), 47.9 ± 10.4	RA: 231	Not stated	NA
Foocharoen et al, 2012 (115)	Switzerland	Quantitative longitudinal single group survey	Multinational database of EUSTAR centers with data collected at baseline	130, male (100), median age 52.3 (IQR 45.1–61.5)	SSc: 130	Median (IQR) 7.0 (3.7–11.9)	NA
Frikha et al, 2014 (74)	Tunisia	Quantitative longitudinal single group survey	Department of internal medicine in Sfax-Tunisia University Hospital with data collected at baseline	10, female (100), 52.4 ± 8.2	SSc: 10	7.7 ± 7.7	NA
Gallinaro et al, 2012 (64)	Brazil	Quantitative cross-sectional controlled cohort survey	Outpatient SpA clinic, university hospital	32, female (12.5), 47.4 ± 19.3	AS: 32	13.7 ± 9.7	32, male (87.5), 38.4 ± 14.3
Garcia Morales et al, 2013 (70)	Spain	Quantitative cross-sectional controlled cohort survey	Systemic autoimmune diseases unit of Hospital of San Cecilio of Granada	65, female (100), 9.0 ± 10.8	AS: 65	7.2 ± 7.4	55, female, 35.7 ± 11.3
Hari et al, 2015 (80)	Not stated	Quantitative cross-sectional controlled cohort survey	Not stated	60, female (100), 49.9 ± 9.3	RA: 60	Median (IQR) 6 (3–10)	40, female, 45.0 ± 9.2
Healey et al, 2009 (60)	UK	Quantitative cross-sectional single group survey	Ten site-specific NHS trust hospitals	612, female (28.4), 50.8 ± 12.2	AS: 612	17.3 ± 11.7	NA
Helland et al, 2008 (92)	Norway	Quantitative cross-sectional single group survey	Postal questionnaires to patients in ORAR	830, female (74), 58.5 ± 14.2	RA: 830	13.4 ± 10.3	NA
Helland et al, 2011 (93)	Norway	Qualitative study (interviews and focus groups)	Rheumatology clinic, tertiary hospital	23, female (43), 44.2 ± 10.5	RA: 11 (48); AS: 7 (30); PsA: 4 (17); JIA: 1 (4)	13.6 ± 10.2	NA
Hill et al, 2003 (8)	UK	Mixed study (quantitative, cross-sectional single group survey and free text questionnaires)	Two consecutive rheumatology outpatient clinics at a large teaching hospital	57, female (82), 58, age range 36–75	RA: 57	Median (IQR) female: 1.5 (3.0–6.3) male: 5 (3.2–6.3)	NA

(Continued)

Table 1. (*Cont'd*)

Study	Country	Design	Setting	IA group, no., sex (%), age mean ± SD years	Type of IA, no. (%)	Disease duration†	Control group, no., sex (% when given), age mean ± SD years
Impens et al, 2009 (61)	US	Quantitative cross-sectional single group survey	Outpatient clinic of the scleroderma program of a university hospital	101, female (100), 47.5 (no range/SD/IQR)	SSc: 101	Not stated	NA
Isik et al, 2017 (89)	Turkey	Quantitative cross-sectional controlled cohort survey	State university hospital	46, female (100), 40.4 ± 5.1	SSc: 46	Median (range) 5.3 (3–8)	47, female, 39.8 ± 3.2
Josefsson et al, 2012 (27)	Sweden	Quantitative cross-sectional single group survey	Two rehabilitation clinics in nontertiary hospital	150, female (81), 56, age range 19–77	RA: 150	Median (range) female: 15 (2–50) male: 10 (1–20)	NA
Khnaba et al, 2016 (86)	Morocco	Quantitative, cross-sectional single group survey	Ei Ayachi University Hospital	60, female (100), 45.2 ± 8.8	RA: 60	Median (range) 5.7 (3.1–10.6)	NA
Kobelt et al, 2012 (94)	France	Quantitative cross-sectional controlled cohort survey	French patient association ANDAR	1,272, female (84), 63.8 ± 12.4	RA: 1,272	19.0 ± 11.6	70, female (77), 59.6 ± 11.7
Levis et al, 2012 (95)	Canada and France	Quantitative cross-sectional controlled cohort survey	Database of women from CSRG registry and general population sample from the Adult Twins UK registry	730, female (100), 57.0 ± 11.3	SSc: 730	12.8 ± 9.7	1,498, female, 55.4 ± 11.5
Majerovitz et al, 1994 (9)	Not stated	Quantitative cross-sectional controlled cohort survey	Practices of 11 rheumatologists affiliated with a major metropolitan tertiary hospital	113, female (72.6), 57.0 (no range/SD/IQR)	RA: 90 (79.6); Polymyalgia rheumatic, temporal arteritis, vasculitis, polymyositis, dermatomyositis, SSc, and mixed connective tissue disease: 23 (20.4)	Not stated	74, female (50), 53.6 (no range/SD/IQR)
Oksel et al, 2014 (75)	Turkey	Qualitative study (semistructured interviews)	Rheumatology polyclinic, university hospital	20, female (100), 50.9 ± 10.0	SSc: 20	8.8 ± 7.6	NA
Önem et al, 2014 (76)	Turkey	Quantitative cross-sectional controlled cohort survey	Rheumatology outpatient unit at a Sisli Etfal training and research hospital	47, female (100), 37.4 ± 7.2	RA: 47	4.8 ± 4.6	45, female, 37.4 ± 6.1
Ostlund et al, 2015 (81)	Sweden	Qualitative study (semistructured interviews)	Informants' home or workplace, or the hospital or university	45, female (53), age range 20–63	RA: 45	Not stated	NA

(Continued)

Table 1. (*Cont'd*)

Study	Country	Design	Setting	IA group, no., sex (%), age mean ± SD years	Type of IA, no. (%)	Disease duration†	Control group, no., sex (% when given), age mean ± SD years
Özgül et al, 2006 (21)	Not stated	Quantitative, cross-sectional single group survey	Not stated	167, male (100), 23.9 ± 3.0	AS: 167	0–5 years: 37.7%, 6–10 years: 36.6%, 11–15 years: 15.8%, >15 years: 9.9%	NA
Ozkorumak et al, 2011 (63)	Turkey	Quantitative cross-sectional controlled cohort survey	Physical medicine and rehabilitation department, Karadeniz Technical University	43, male (100), 36.3 ± 8.8	AS: 43	Not stated	43, male, 36.5 ± 6.5
Pendeke et al, 2016 (87)	Scotland, England, and Wales	Qualitative study (semistructured interviews)	Various community hospital locations in Scotland, England, and Wales with the help of Lupus UK	8, male (100), age range 20–69	SLE: 8	11.5 (SD not stated)	NA
Pirildar et al, 2004 (116)	Not stated	Quantitative cross-sectional controlled cohort survey	Not stated	65, male (100), 36 ± 8.1	AS: 65	12.2 ± 6.4	65, male, 37 ± 5.2
Priori et al, 2015 (85)	Italy	Quantitative cross-sectional controlled cohort survey	Systemic sclerosis clinic, university hospital	24, female (100), 50.4 ± 12.0	SS: 24	Not stated	24, female, 47.0 ± 13.3
Rezvani et al, 2012 (65)	Turkey	Quantitative cross-sectional controlled cohort survey	Rheumatology outpatient clinic of a tertiary care center	39, male (100), 38, age range 27–52	AS: 39	Median (IQR) 4.4 (0–19.3)	27, male, 30, age range 23–45
Rosato et al, 2014 (77)	Italy	Quantitative cross-sectional single group survey	Scleroderma center of clinical immunology and rheumatology clinic, tertiary hospital	102, female (100), 51 ± 13	SSc: 102	8 ± 6	NA
Rostom et al, 2013 (71)	Not stated	Quantitative cross-sectional single group survey	Not stated	110, male (100), 38.9 ± 12.5	AS: 110	Median (IQR) 9 (0–40)	NA
Saadat et al, 2015 (82)	Iran	Quantitative cross-sectional controlled cohort survey	Rheumatology ward, Baquiyatallah tertiary hospital	90, female (100), 40.1 ± 4.1	RA: 90	Not stated	110, female, 37.5 ± 2.1
Sanchez et al, 2016 (88)	France	Quantitative cross-sectional single group survey	Department of internal medicine, Cochin Hospital	292, female (82.2), 55.9 ± 14	SS: 292	8.6 ± 7.7	NA
Santana et al, 2017 (90)	Brazil	Quantitative cross-sectional controlled cohort survey	Rheumatology unit, university hospital	40, male (100), 45.8 ± 11.4	AS: 40	Median (IQR) 18 (8.2–20.0)	40, male, 46.0 ± 11.1

(Continued)

Table 1. *(Cont'd)*

Study	Country	Design	Setting	IA group, no., sex (%), age mean ± SD years	Type of IA, no. (%)	Disease duration†	Control group, no., sex (% when given), age mean ± SD years
Sariyildiz et al, 2013 (117)	Turkey	Quantitative cross-sectional controlled cohort survey	Two centers of physical medicine and rehabilitation at university hospitals	70, male (100), 36.4 ± 7.4	AS: 70	9.9 ± 6.9	60, male, 35.2 ± 7.7
Sariyildiz et al, 2013 (22)	Turkey	Quantitative cross-sectional controlled cohort survey	Two centers of physical medicine and rehabilitation at university hospitals	37, female (100), 34.1 ± 7.0	AS: 37	8.6 ± 7.4	33, female, 33.5 ± 6.2
Schouffoer et al, 2009 (96)	Netherlands	Quantitative cross-sectional controlled cohort survey	Two academic rheumatology outpatient university hospitals	37, female (100), 45.6 ± 9.5	SSc: 37	6.5 ± 8.8	37, female, 43.3 ± 8.0
Seawell et al, 2005 (58)	US	Quantitative cross-sectional controlled cohort survey	Postal questionnaire to women listed in database of NENYLFA	54, female (100), 47.4, age range 22–75	SLE: 54	Not stated	29, female, 44.7, age range 22–67
Tseng et al, 2011 (97)	Taiwan	Quantitative cross-sectional controlled cohort survey	Rheumatology outpatient clinic, general hospital	279, female (100), 37.5 ± 10.2	SLE: 279	9.5 ± 6.4	1,580, female, 34.8 ± 8.5
Ugurlu et al, 2014 (99)	Not stated	Quantitative cross-sectional controlled cohort survey	Not stated	64, female (100), 40.1 ± 7.5	SS: 64	Not stated	32, female, 37.4 ± 7.0
van Berlo et al, 2007 (19)	Netherlands	Quantitative cross-sectional controlled cohort survey	Departments of rheumatology in 3 hospitals (large regional hospital, university hospital, and a small hospital serving mainly a rural area)	213, female (63.8), 52.7 ± 11.8	RA: 231	13.1 ± 9.8	107, female (49), 49.4 ± 10.8
van Nimwegen et al, 2015 (100)	Not stated	Quantitative cross-sectional controlled cohort survey	Postal questionnaire to patients in general practitioner's office	46, female (100), 46.3 ± 10.5	SS: 46	Median (IQR) 7 (4–14)	43, female, 44.4 ± 11.3
Yilmaz et al, 2012 (98)	Turkey	Quantitative cross-sectional controlled cohort survey	Department of physical medicine and rehabilitation in research hospital	203, female (100), 40.9 ± 7.3	RA: 203	5.9 ± 5.0	108, female, 40.1 ± 8.1

* IA = inflammatory arthritis; RA = rheumatoid arthritis; PsA = psoriatic arthritis; AS = ankylosing spondylitis; SpA: spondyloarthritis; IBD = irritable bowel disease; NA = not applicable; SSc = systemic scleroderma/systemic sclerosis; SLE = systemic lupus erythematous; IQR = interquartile range; EUSTAR = European League Against Rheumatism Scleroderma Trial and Research Group; ORAR = Oslo Rheumatoid Arthritis Register; JIA = juvenile idiopathic arthritis; ANDAR = Association Nationale de Défense contre l'Arthrite Rhumatoïd; CSRG = Canadian Scleroderma Research Group; NENYLFA = North East New York Lupus Foundation of America.
† Values are in years, given as mean ± SD unless stated otherwise.

Table 2. Outcome and risk-of-bias assessment from quantitative studies*

Study	FSFI, mean ± SD		IIEF, mean ± SD		Other outcome measure, scale (range); interpretation†	Overall risk of bias‡
	IA group	Control	IA group	Control		
Abda et al, 2016 (83)	–	–	–	–	Sexual disability and satisfaction questionnaire derived from HAQ disability index (grade range 0–3, where lower grades indicate better sexual function: 0 = able, 1 = mild, 2 = moderate, 3 = completely unable). IA group: grade 0: 42 (21); grade 1: 90 (45); grade 2: 34 (17); grade 3: 34 (17)	5
Aguiar et al, 2014 (72)	–	–	–	–	Custom questionnaire; continuous scale (0–100, higher score associated with higher satisfaction with sexual life): IA mean ± SD 52.3 ± 31.0; control 57.6 ± 29.9	6
Akkurt et al, 2016 (84)	22.1 ± 5.5§	31.4 ± 3.0§	–	–	–	5
Aras et al, 2013 (66)	19.1 ± 4.7§	24.6 ± 4.2§	–	–	–	4
Bal et al, 2011 (62)	–	–	23.8 ± 7	25.1 ± 6.6	–	5
Bhadauria et al, 1995 (113)	–	–	–	–	Sexual function and semiquantitative sexual satisfaction index. Decreased desire: IA 39.6 (66); control 13.8 (60); decreased frequency of intercourse: IA 43.8 (73); control 16.8 (73); decreased orgasms: IA 31.2 (52)§; control 3.9 (17)§; decreased intensity of orgasms: IA 31.8 (53)§; control 2.3 (10)§	6
Bongi et al, 2013 (67)	18.0 ± 12.3	21.2 ± 11.5	–	–	–	4
Coskun et al, 2014 (73)	24.5 ± 6.0§	32.3 ± 3.5§	–	–	–	4
Daleboudt et al, 2013 (68)	–	–	–	–	PDSBE and MIS-SFQ; patients reporting negative influence on sexual functioning: IA 52.5 (49.1)	5
Demir et al, 2013 (69)	23.7 ± 5.6	23.1 ± 5.9	–	–	–	4
Dhakad et al, 2015 (79)	–	–	20.5 ± 7.1§	24.9 ± 3.8§	–	5
Dincer et al, 2007 (59)	–	–	–	–	BMSFI (total 0–44, lower scores indicate poor sexual function; no threshold score provided): IA mean ± SD 28.9 ± 8.4§; control 33.3 ± 7.6§	6
Dorner et al, 2018 (91)	–	–	–	–	Custom questionnaire; some difficulty with intercourse: IA 31.2 (57.7)	6
Druley et al, 1997 (114)	–	–	–	–	QMI and a self-administered questionnaire designed for study (all values here for the IA group only); sexual intercourse: engaged: 54.8 (74), initiated: 34.8 (47), avoided: 41.4 (56); foreplay: engaged: 51.1 (69), initiated: 40.0 (54), avoided: 39.2 (53)	4
El Miedany et al, 2012 (7)	23.2 ± 6.4	–	–	–	SHIM for erectile dysfunction (all values here for the IA group only); mild: 18 (36.7), mild to moderate: 16 (32.7), moderate: 13 (26.5), severe: 2 (4.1)	5
Foocharoen et al, 2012 (115)	–	–	–	–	IIEF for erectile dysfunction (all values here for the IA group only); none: 23 (17.7), mild: 25 (19.2), mild-moderate: 26 (20.0), moderate: 14 (10.8), severe: 40 (30.8)	4
Frikha et al, 2014 (74)	14.2 ± 7.8	–	–	–	–	6
Gallinaro et al, 2012 (64)	–	–	–	–	Sexual activity questionnaire; frequency of intercourse ≥2/week: IA 21.3 (66.7)¶; control 24 (85.7)¶; pain after sexual relationship: IA 19.8 (61.9)¶; control 3 (10.7)¶; sexual relationship interrupted due to pain: IA 3 (9.5)¶; control 0 (0)¶; fatigue: IA 10.6 (33.3)¶; control 8 (28.6)¶; orgasm: IA 22.8 (71.4)¶; control 21 (75.0)¶; sexual satisfaction: IA 27.5 (85.8)¶; control 26 (92.9)¶; complete sexual act: IA 22.8 (71.4)¶; control 25 (89.3)¶; duration of sexual intercourse (minutes): IA 6.1 (19.2)¶; control 9.6 (34.2)¶	7
Garcia Morales et al, 2013 (70)	24.5 ± 8.0§	27.6 ± 7.7§	–	–	–	1
Hari et al, 2015 (80)	24.5 ± 7.8§	18.3 ± 9.1§	–	–	–	5
Healey et al, 2009 (60)	–	–	–	–	Custom questionnaire, extent AS affected intimate/sexual relationships: not at all or a little bit: IA 342 (62); moderately to extremely: IA 210 (38)	2

(Continued)

Table 2. (*Cont'd*)

Study	FSFI, mean ± SD		IIEF, mean ± SD		Other outcome measure, scale (range); interpretation†	Overall risk of bias‡
	IA group	Control	IA group	Control		
Helland et al, 2008 (92)	–	–	–	–	Item 15 of the 15D generic/standardized HRQoL instrument (all values here for the IA group only); no effect: 257.3 (31), slight effect: 315.4 (38), considerable effect: 174.3 (21), almost impossible: 24.9 (3), impossible: 58.1 (7)	5
Hill et al, 2003 (8)	–	–	–	–	Questionnaire previously developed for patients with arthritis (ref. 124) reporting impact of RA on relationship (all values here for the IA group only); not applicable: 14 (25), no change: 23 (56), changed: 18 (44)	4
Impens et al, 2009 (61)	24.9 ± 6.7§	30.5 ± 5.3§	–	–	–	5
Isik et al, 2017 (89)	17.2 (SD not reported)§	27.4 (SD not reported)§	–	–	–	3
Josefsson et al, 2012 (27)	–	–	–	–	Questionnaire developed by authors (all values here for the IA group only); good or very good sexual well-being: 55.5 (37), RA had negatively affected sexual health: 55.5 (37), reduction in sexual desire due to RA: 93 (62), continuing experience of decreased sexual desire: 81 (54), decreased sexual satisfaction due to RA: 64.5 (43), weak or no sexual satisfaction: 28.5 (19)	8
Khnaba et al, 2016 (86)	18.3 ± 9.1	–	–	–	–	4
Kobelt et al, 2012 (94)	–	–	–	–	Self-assessed impact of RA on sexual activity questionnaire developed for study (all values here for the IA group only); RA an obstacle for intimate relationship: 864.3 (68), RA an obstacle for sexual relationships: 966.0 (76), RA to be a major obstacle for intimate relationships: 368.6 (29), RA to be a major obstacle for sexual relationships: 419.4 (33)	6
Levis et al, 2012 (95)	–	–	–	–	9-item abbreviated version of 19-item FSFI; sexually active: IA 296 (41); control 956 (64); sexually impaired: IA 181 (61); control 420 (44)	6
Majerovitz et al, 1994 (9)	–	–	–	–	SDS (scale 5–25, higher scores indicating greater sexual dissatisfaction); IA M: 11.2 ± 4.4¶, F: 13.9 ± 4.8¶; control M: 10.8 ± 3.6¶, F: 13.1 ± 4.3¶	8
Önem et al, 2014 (76)	–	–	–	–	GRISS (scale 0–96, higher scores indicating greater sexual dissatisfaction); IA mean ± SD 36.7 ± 15.6; control 34.2 ± 14.2	6
Özgül et al, 2006 (21)	–	–	–	–	SF-36 (all values here for the IA group only); sexual intercourse: had troubles 88 (52.7), a little 40.4 (24.2), somewhat 36.7 (22.1), moderately 8.9 (5.3), very 1.8 (1.1); sexual satisfaction: had troubles 89 (53.3), a little 47.3 (28.3), somewhat 29.1 (17.4), moderately 9 (5.4), very 3.3 (2.2); sexual desire: had troubles 78.5 (47.0), a little 46.1 (27.6), somewhat 23.9 (14.3), moderately 8.5 (5.1), very 0	6
Ozkorumak et al, 2011 (63)	–	–	–	–	GRISS (scale 0–96, higher scores indicating greater sexual dissatisfaction); IA mean ± SD 5.1 ± 1.6§; control 4.0 ± 1.7§	3
Pirildar et al, 2004 (116)	–	–	23.1 ± 7.5§	27.1 ± 6.3§	–	4
Priori et al, 2015 (85)	23.1 ± 7.5§	27.1 ± 6.3§	–	–	–	2
Rezvani et al, 2012 (65)	–	–	19.1 ± 7.3	26.1 ± 8.8	–	3
Rosato et al, 2014 (77)	18.5 ± 9.8	–	–	–	FSDS-R (scale 0–30, score ≥11 indicates sexual distress); IA mean ± SD 10.2 ± 10	4
Rostom et al, 2013 (71)	–	–	–	–	MSSCQ (all values here for the IA group only); unsatisfied with sexual activity: 32 (44); erectile dysfunction: 30 (41); orgasmic trouble: 28 (38.4)	7
Saadat et al, 2015 (82)	–	–	–	–	MSSCQ (range not stated, lower scores indicative of poorer sexual function) mean ± SD; desire: IA 17.6 ± 5.5; control 17.9 ± 3.8; sensation: IA 12.2 ± 4.5§; control 13.7 ± 4.5§; lubrication: IA 6.2 ± 2.1§; control 6.9 ± 2.1§; cognition: IA 6.2 ± 2.0; control 6.3 ± 1.7; orgasm: IA 9.5 ± 3.3§; control 10.4 ± 2.9§; pain: IA 10.9 ± 1.9§; control 10.1 ± 2.3§; enjoyment: IA 21.3 ± 7.5§; control 23.8 ± 5.9§; partner related: IA 7.7 ± 2.4§; control 8.5 ± 1.8§	5

(Continued)

Table 2. (*Cont'd*)

Study	FSFI, mean ± SD		IIEF, mean ± SD		Other outcome measure, scale (range); interpretation†	Overall risk of bias‡
	IA group	Control	IA group	Control		
Sanchez et al, 2016 (88)	16.3 ± 6.2	–	16 ± 5.3	–	–	5
Santana et al, 2017 (90)	–	–	22.0 (median, SD not reported)§	29.0 (median, SD not reported)§	–	4
Sariyildiz et al, 2013 (117)	–	–	23.8 ± 5.3§	27.0 ± 2.1§	–	4
Sariyildiz et al, 2013 (22)	23.8 ± 4.1§	28.3 ± 4.7§	–	–	–	4
Schouffoer et al, 2009 (96)	20.6 ± 9.4§	27.6 ± 6.2§	–	–	–	4
Seawell et al, 2005 (58)	–	–	–	–	SDS; (scale 5–25, higher scores indicate greater dissatisfaction) mean ± SD; IA 14.2 ± 5.4; control 13.6 ± 3.2	5
Tseng et al, 2011 (97)	25.7 ± 4.7§	26.8 ± 4.5§	–	–	–	3
Ugurlu et al, 2014 (99)	16.6 ± 7.9§	23.3 ± 5.9§	–	–	–	5
van Berlo et al, 2007 (19)	–	–	–	–	QSD; mean ± SD; higher scores = greater intercourse frequency and sexual satisfaction, frequency sexual daydreams/fantasies (1–7): IA: M 2.4 ± 1.5, F 1.4 ± 0.9§; control: M 3.1 ± 1.5, F 1.9 ± 1.3§; frequency desire for sexual contact with partner (1–7): IA: M 3.2 ± 1.6§, F 2.9 ± 1.4; control: M 4.1 ± 1.4§, F 3.4 ± 1.3; frequency sexual contact (1–7): IA: M 2.8 ± 1.5, F 3.2 ± 1.5; control: M 3.5 ± 1.3, F 2.7 ± 1.4; frequency masturbation (1–7): IA: M 1.8 ± 1.3, F 1.2 ± 0.8§; control: M 2.4 ± 1.5, F 1.8 ± 0.9§; frequency sexual contact against will (1–7): IA: M 1.0 ± 0.0, F 1.2 ± 0.6: control: M 1.0 ± 0.0, F 1.1 ± 0.4; as exual satisfaction (1–5): IA: M 3.6 ± 0.9, F 2.7 ± 0.8; control: M 3.6 ± 0.8, F 3.7 ± 0.9	7
van Nimwegen et al, 2015 (100)	20.6 (SD not reported)§	30.3 (SD not reported)§	–	–	–	6
Yilmaz et al, 2012 (98)	–	–	–	–	IFSI, scale (5–45, higher scores indicate better sexual function); mean ± SD IA: 22.8 ± 9.0§; control: 34.6 ± 8.3§	5

* The 2 most common outcomes are presented (FSFI and IIEF), as well as other outcome measures reported in the included studies. FSFI = Female Sexual Function Index, score range: 2–36, Scoring direction: Sexual dysfunction indicated by score ≤26.5; IIEF = International Index of Erectile Function scoring system, score range: 0–30, Scoring direction: Sexual dysfunction indicated by score ≤25 (43,123); IA = inflammatory arthritis; HAQ = Health Assessment Questionnaire; PDSBE = Physical Disability and Sexual and Body Esteem Scale; MIS-SFQ = Medical Impact Scale of the Sexual Functioning Questionnaire; BMSFI = The Brief Male Sexual Function Inventory; QMI = Quality of Marriage Index; SHIM = Sexual Health Inventory for Men; HRQoL = health-related quality of life; RA = rheumatoid arthritis; SDS = Sexual Dissatisfaction Scale; GRISS = Golombok Rust Inventory of Sexual Satisfaction; SF-36 = 36-item Short Form health survey; FSDS-R = Female Sexual Distress Scale Revised; MSSCQ = Multidimensional Sexual Self-Concept Questionnaire; QSD = questionnaire for screening sexual dysfunctions; IFSI = Index of Female Sexual Function.
† Values are the number (%) unless indicated otherwise.
‡ Based on Hoy et al (2012) risk-of-bias tool (range 0–10): low 0–3; moderate 4–6; high 7–9.
§ Statistically significant difference ($P < 0.05$) reported between groups in the study.
¶ Groups were not compared using statistical analysis.

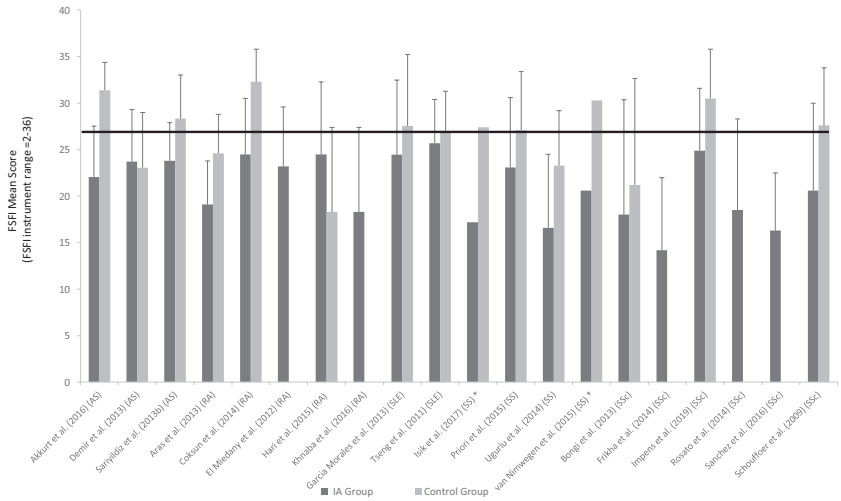

Figure 2. Mean Female Sexual Function Index (FSFI) scores and SDs (error bars). Studies are grouped by type of inflammatory arthritis. Sexual dysfunction is indicated by an FSFI score of ≤26.5, indicated by the horizontal line. AS = ankylosing spondylosis; RA = rheumatoid arthritis; SLE = systemic lupus erythematous; SS = Sjögren's syndrome; SSc = systemic sclerosis; IA = inflammatory arthritis. *Isik et al (89) and van Nimwegen et al (100) did not report SDs.

mean scores (62,79). One study did not involve comparison with a control group, although the mean IIEF score remained lower compared to mean scores of inflammatory arthritis groups across other studies (88). Comparing outcomes by disease, a population with SSc had the lowest mean IIEF score (88), followed by AS groups (62,65,79,90,116,117), while those with RA appeared to have the highest IIEF mean score (73).

Twenty-six studies (47.3%) utilized outcome measures that included other validated and reliable tools, shortened versions of existing tools, or customized tools for that specific study (7–9,19,21,27,58–60,63,64,68,71,72,76,77,82,83,91,92,94,95,98,113–115). All studies identified sexual dysfunction among their inflammatory arthritis groups, but few commented on the impact of inflammatory arthritis on intimate relationships (8,60,94). In those that did, only the prevalence of disrupted relationships was explored, which was reported by 38% of men with AS (60) and 44–76% of males and females with RA (8,94). Among the 13 studies (50%) that compared outcomes with control groups, impaired sexual function was more consistently reported by patients with inflammatory arthritis, compared to controls (9,19,58,59,63,64,72,

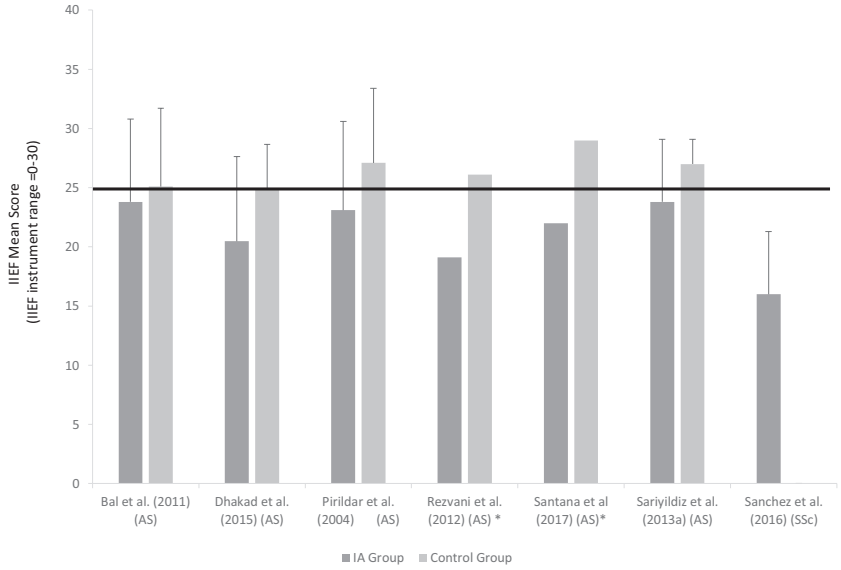

Figure 3. Mean International Index of Erectile Function (IIEF) scores and SDs (error bars). Studies are grouped by type of inflammatory arthritis. Sexual dysfunction is indicated by an IIEF score of ≤25 (43,120), indicated by the horizontal line. AS = ankylosing spondylosis; SSc = systemic sclerosis; IA = inflammatory arthritis. *Because Rezvani et al (65) and Santana et al (90) did not report mean scores or SDs, median scores for these studies are shown instead.

76,82,90,95,98,113). The scope of sexual dysfunction measured in these studies involved the degree of sexual or erectile dysfunction (7,9,21,27,58–60,63,76,77,83,93,94,98,114,115,121), the prevalence of sexual dysfunction (8,68,71,91,92,95), the prevalence of patients engaging, initiating, and avoiding intercourse and foreplay (114), satisfaction with sexual life (72), and individual domains of sexual function (including desire, masturbation, fantasies, frequency, fatigue, pain, sensation, lubrication, orgasm, intensity of orgasms, and overall sexual satisfaction) (19,64,82,113).

Subject data collection (7,9,19,21,22,27,58–63,65–67, 69–74,76,77,79,80,82–84,86,88–92,96,97,99,113–117), acceptable case definition (7,9,19,21,22,58–60,62–74,76,77,79, 80,82–84,86,88–92,94–98,113–117), mode of data collection (7–9,19,21,22,27,58–67,69–74,76,77,79,80,82–84,86,88–92,94–98,113–117), a short prevalence period (9,19,21,22,58,60–63,65–67,69–74,76,77,80,82–84,86,88–91,94–98,116,117), and validity of measurement tools (7, 9, 19, 21, 22, 58, 60–63, 65–67, 69–71, 73, 77, 79, 80, 82, 84, 86, 88–90, 94–98, 115–117) were the most common shortfalls across included studies. Most quantitative studies (n = 37 [75.5%]) were assessed as having a moderate risk of bias (7,8,21,22,58,59,61,62,66–69,72–74,76,77,79,80,82–84,86,88,90–92,94–96,98,99,113–117). Only 7 of the studies (14.3%) were considered at low risk of bias (60,63,65,70,85,89,97), while 6 (12.2%) were assessed as having a high risk of bias (9,19,27,64,71,100). The risk of bias in these high-risk studies was primarily related to internal validity considerations (mode of data collection, case definition, reliable and acceptable diagnosis, and short period for determining prevalence) (9,19,27,64,100).

Metasynthesis of qualitative data. Metasynthesis outcomes for the 6 eligible qualitative studies are summarized in Table 3. Two key themes were identified, supported by several subthemes.

Theme 1: impaired sexual function. Subtheme analysis demonstrated that sexual function was affected by pain, reduced sexual desire, erectile dysfunction, and fatigue, along with the same stressors that affect the general population, such as stress, and other general life concerns (8,78,87,93,118). Individuals with inflammatory arthritis reported that they typically changed the positions previously adopted during intercourse, assuming a more passive role to reduce pain (78,93). Pain was associated with a fear of interrupted intercourse or intercourse being postponed (78,93). The level of sexual dysfunction often varied with flares in disease activity, but also with time of day, because pain and fatigue were more likely to affect sexual dysfunction during the evening (93,118). Erectile dysfunction largely accounted for sexual dysfunction in males, which caused frustration, shock, stress, and a sense of emasculation (93,118). A negative body image, reduced desire for intercourse, and erectile dysfunction all contributed to an altered sense of sexuality across both sexes (87,93,118).

Theme 2: compromised intimate relationships. Intimate relationships tended to transition toward a more caring and less physical nature as the importance of sexual intercourse was reduced, particularly during disease flares (93). Some partners had greater acceptance and understanding of the impact that inflammatory arthritis had on sexual function than others, assisting to strengthen relationships between partners (8). Others found that their partners poorly understood the impact of inflammatory arthritis on their ability to engage in intercourse, creating tension and fear in their relationships (75,93,118). Despite the sexual dysfunction associated with inflammatory arthritis, women often felt pressured to maintain a normal sex life to prevent relationships being compromised by inflammatory arthritis (8,93). Poor body image reduced sexual desire in both male and female populations and restricted individuals from finding partners (93).

Quality assessment of the qualitative studies is summarized in the Supplementary materials, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23857/abstract. Many of the qualitative studies were considered to have a risk of bias due to lack of consideration of the relationship between researchers and their participants (8,75,78,87,93), ethical issues (93), or a failure to clearly state the research aims (87).

Confidence in the metasynthesis findings was evaluated based on the 4 domains of the GRADE-CERQual approach (see Supplementary materials, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23857/abstract). Overall, we identified 11 key findings based on the summary of results from primary studies (Table 3); 2 findings were associated with a high level of confidence that the review findings were a reasonable representation of the phenomenon of interest, while 3 were rated as moderate confidence and 3 were rated as very low confidence.

DISCUSSION

We identified consistent evidence (albeit of varying methodologic quality) highlighting an association between inflammatory arthritis and impacts on intimate relationships and sexual function for both sexes. Individuals living with inflammatory arthritis consistently demonstrated a higher prevalence of sexual dysfunction compared to their healthy peers, although these estimates tend to be crude and are not adjusted for potential confounders. For both sexes, disease-related factors contributed to sexual dysfunction (including pain, fatigue, and mobility restrictions) and reduced sexual desire, as well as nondisease-related factors that typically affect the general population. Erectile dysfunction and its emotional sequelae largely accounted for sexual dysfunction in males, while females experienced pressure to continue intimate relationships despite their sexual dysfunction, causing stress in relationships (8,93,118).

Table 3. Metasynthesis of qualitative data*

Theme and subthemes and metasynthesis summary	Findings from primary study	Supporting excerpts
Impaired sexual function		
1.1 Pain (78,93,118): Sexual function was affected by pain, reduced sexual desire, erectile dysfunction, and fatigue, along with the same stressors that affect the general population such as stress, education, and concerns. People with IA had typically changed the positions they previously adopted during intercourse, such as assuming a more passive role to reduce pain caused by movement and positions.	Pain limited positions and movements during sexual intercourse, resulting in interrupted or postponed sexual intercourse. Pain easily interrupted sexual intercourse for people with IA. This then instilled fear in people with IA that they would let their partner down. Some women with IA needed to be in control during intercourse to reduce pain, while others reported playing a more passive role to reduce pain. Men were frustrated with having to play a passive role during intercourse to reduce pain. Sexual activity varied depending on pain, as pain often restricted positions used and time of day people with IA could be sexually active.	"My sex life has been very affected. Because of the very severe pain, I cannot have sex. I cannot adapt myself to sex because of the pain I feel. In fact, to lie down in bed, even for a very short time, increases my pain." [male] (78) "I encounter difficulty with sex because I cannot move my thighs very much because of pain. For that reason, I prefer easy positions in bed." [female] (78) "I have been forced to interrupt sex sometimes… It's always in the back of my mind; will I be able to carry it through? I worry that it will hurt his feelings or make me feel bad, because I have initiated something that I couldn't follow through on." [female] (93) "If I am in a lot of pain, it's better that I am in control, that I take the lead. Then we do different things or use different positions, which might mean that I am on top or that I make sure I don't get hit or bumped. It is important that I have control over the movements." [female] (93) "My experience is that you really want to be active, but you end up being passive, and that's not very exciting, is it? It does something with your self-esteem or the sense of being attractive." [female] (93) "It's irritating [being passive]. Feeling that you can't do exactly what you want for yourself or to make it best for both of us." [male] (93) "In other words I have a lot of pain… you don't think about being intimate then, not that day anyway…except I think it's important, on the other hand I think it's important with closeness, hugs, in other words that you, that you kiss and hug but it can stop there, you don't have to go further… sure, I can have pain then, when I go to bed I can have pain even then, so I mean sure, it limits me. It's probably not the first thing you think about when you have sex with someone, if you have pain I mean." [female] " [sex life] is limited sometimes… sometimes it works well and sometimes it doesn't work at all, when I have pain it doesn't work and then, unfortunately, that's what's a bit annoying with it, she thinks [the wife] then, amongst other things." [male] "She knows I have pain in my hands so that she can't have… can't take at any rate, you know… Especially if you're lying and hugging, then your hands can get squeezed, you know. And that can really hurt. I'm more sore at night… because I've been busy and maybe worked, so maybe I'm more sensitive than in the mornings." [male]
1.2 Erectile dysfunction (87,93,118): Erectile dysfunction largely contributed to male sexual dysfunction, which caused frustration, shock, stress, and emasculation. Negative body image, reduced desire for intercourse, and erectile dysfunction all contributed to an altered sense of sexuality in men.	Men were particularly frustrated and stressed with the impact their disease had on erections and how to explain this to partners. Men were often shocked by the occurrence of erectile dysfunction and its threat to their masculinity.	"Getting an erection, everyone knows it's a really touchy area for men. I didn't think I would care about it so much, but I did. I would not have been so upset if it had been because my hip was so bad or my arm was like that." [male] (93) "I met a girl last year, and I didn't damn well know how I was going to bring it up because I knew he wasn't working as well as he had before 'John Thomas,' but it petered out, because I explained to her that I had a bit of a problem with erections… he's not dead… it works of course, but dammit." [male] "Sexual relations with my wife have suffered immensely… As a husband I'm frustrated because it's taken away my ability to perform for the wife sexually. I did not see this coming at all. It's depressing, being a man on paper, not one defined by their ability." [male] (87) "Where it matters most as a husband I have failed her. I have not been able to make love to my wife owing to erectile dysfunction caused by this condition. She probably sees me as half a man, if at all." [male] (87)
1.3 Fatigue and stressors (8,93,118): Fatigue reduced sexual desire and consequently the frequency of sexual intercourse, but this wasn't an issue for some couples in long-term relationships.	Fatigue reduced sexual desire and consequently the frequency of sexual intercourse. This was not an issue for some couples in long-term relationships. Sex life was not affected by IA alone, but also by the same stressors that affect the general population.	"Sometimes I am so tired and in pain that sex is the last thing I think about. A cuddle is just as nice." [female] (8) "I believe that you possibly do get more tired and need to go to bed early at night and you might choose to get a good night's sleep instead [of having sex]. Well, several of my medicines do list this as a side-effect saying that it can affect sexual desire, but that's hard to judge, I don't really know, I can't say, well, yes it is tiredness that affects me most… but I don't think my husband thinks like that, like he needs to take my illness into consideration, so it is the same thing there, because I don't feel that I am suffering from an illness he doesn't either need to treat me as being ill." [female] "Sexual life is so incredibly susceptible to everything, there's so much in life that affects it; stress, education, and concerns. So my experience is that many are concerned that they do not want too much put on the disease. There is so much in life in general that affects sexuality… okay, there are some drawbacks with it [the disease], but we experience many of the same stressors as healthy people do." [female] (93)

(Continued)

Table 3. (*Cont'd*)

Theme and subthemes and metasynthesis summary	Findings from primary study	Supporting excerpts
1.4 Sexual desire (8,93): Poor body image reduced sexual desire in both males and females with IA and restricted people with IA from finding partners in the first place.	IA reduced desire for intercourse, causing substantial guilt for some people. A loss of desire for intercourse led to a sense of impaired masculinity. Body image, particularly for females, reduced desire for physical intimacy due to not feeling attractive.	"The disease has had a huge impact on my sex life. Not in terms of physical problems, but sex drive. It's really reduced." [male] (93) "To some extent. The problem is on my side really. I feel guilty about not being able to pull my weight, etc." [male] (8) "The disease has had a huge impact on my sex life. Not in terms of physical problems, but sex drive. It's really reduced." [male] (93) "In bad periods with a lot of activity, I feel rotten inside and then sex is not foremost in my mind. I feel very unattractive and tend to say no thanks." [female] (93)
1.5 Fluctuations of sexual function with disease activity/flares (93): Disease-related pain was associated with a fear of interrupted intercourse or intercourse being postponed. The level of sexual dysfunction often varied with flares in disease activity as well as the time of day of intercourse. For example, by the end of the day people with IA were often fatigued and experiencing pain.	Sexual ability fluctuated, depending on symptoms associated with IA disease activity. Intercourse was most often interrupted during disease flares. Sexual intercourse was not considered important for people with IA, particularly during disease flares.	"Fluctuations in the disease and symptoms restrict my sex life. Sometimes it poses a problem, very often it doesn't. It's very up and down, there's no pattern." [female] (93) "When you can hardly move, and you have pain in your entire body, sex isn't exactly what's on your mind." [female] (93)
Compromised intimate relationships		
2.1 Reduced frequency of sexual activity (93): Intimate relationships tended to transition toward a caring and less physical nature as the importance of sexual intercourse was reduced, particularly during disease flares.	Reduced importance of sexual life was highlighted. A greater need for caring relationships was identified.	"The only thing I needed was a shoulder to cry on and an arm that cared and didn't mind. Our exciting sex life turned into more of a deeply caring relationship, which was really great." [female] (93)
2.2 Embarrassment and frustration: People with IA were concerned that their partners would not accept them.	People with IA were concerned that their partners would not accept them.	"Especially I think mentally… and you can feel really bad and you think yeah, but think if this continues, that I'm going to feel like this and I'm going to look like this, is he going to accept me then, because sex is a big part of a relationship. I think it affects it a lot, and as I said, then it's how you feel on and off too… yes, it's [fear] that he's going to leave me and then I'll be sad and have low self-esteem also then, it leaves a mark, now I haven't been in a situation where it really has been a disaster, luckily, because I think it really would be, something that would sit emotionally for both of us I think, that the other one would maybe be…yeah. But as my boyfriend then he'd be a little like this, a-ha, how is this actually going to work, will she be able to have sex with me in 2 years? That's how I feel…odd." [female]

(Continued)

Table 3. (*Cont'd*)

Theme and subthemes and metasynthesis summary	Findings from primary study	Supporting excerpts
2.3 Altered self-image and/or sense of confidence in sexuality (75,93,118): People with IA felt that partners did not understand the impact IA had on their loved one's ability to have intercourse. Reduced closeness and intimacy occurred since IA diagnosis due to the perception of poor body image.	People felt that partners did not understand the impact IA had on their loved one's ability to have intercourse. People with IA reported a reduced closeness and intimacy since their diagnosis due to the perception of poor body image. A negative body image perceived by people with IA impaired their sexuality. The impact IA had on body image restricted people from finding partners.	"And I get tired and difficult when I'm with her… you have to try and be considerate all the same, show that… but she always looks at me when I'm in pain… but then she thinks I'm not enough maybe, all the time. If we're sitting and hugging and feeling good, then I don't want to do it, then I'd rather pull away or, more accurately, push her away, unfortunately… I'm a failure. That's why I think she doesn't always accept the disease, but it's just how it is. I think that's the hardest thing right now, that you can't validate your wife when she maybe needs it, but that's always something you have to work on, as long as you have rheumatism anyway." [male] "It had a huge impact on our sex life that he never seemed to understand that I was exhausted or in pain until I couldn't sit down, go to the toilet, or walk. Then he understood, and that hurt my feelings." [female] (93) "My husband has become estranged from me since the diagnosis." [female] (75) "[It is] as if my husband does not consider me a woman." [female] (93) "I can feel very, what shall I say, unsexy, when I can barely even walk, and my hands especially, aren't particularly beautiful, because they have bumps and I can't move them so well back and forth." [female] "It's not easy to find a man… I often think that nobody could love me the way I look now, because I look awful, don't I?" [female] (93)
2.4 Altered relationship with partner (8,78,87,93): Despite the sexual dysfunction associated with IA, women often felt pressured to maintain a normal sex life to prevent relationships being affected by the disease. Some partners had greater acceptance and understanding of the impact IA had on sexual function than others, assisting to strengthen relationships between partners. Conversely, others experienced that their partners poorly understood the impact of IA on their ability to engage in intercourse, creating tension and fear of relationship instability.	Some women felt they had to push themselves to have intercourse despite reduced desire and fatigue, as they feared partners would leave them or didn't want their sexual relationships to be affected by the disease. Some women felt the need to maintain a normal sex life for their partners despite the presence of sexual dysfunction. Some partners had greater acceptance and understanding of the impact IA had on sexual function than others, assisting to strengthen relationships. Conversely, others experienced that their partners poorly understood the impact of IA on their ability to engage in intercourse, creating tension and fear of relationship instability.	"I have pushed myself. Even if I was exhausted, I have made a really big effort. I don't want all the reasons he is with me to disappear." [female] (93) "My husband and I have been married for 30 years and we have always had a loving sexual relationship. He is not overdemanding, which is most probably a good thing, but I do believe it is important, with all my problems, to still have a normal sex life." [female] (8)

* IA = inflammatory arthritis.

Our review demonstrated that studies have primarily assessed the impact of inflammatory arthritis on sexual function using the FSFI and IIEF instruments. All studies using the FSFI showed that inflammatory arthritis populations had a mean score lower than the FSFI threshold of ≤26.55 (119), indicating greater prevalence of sexual dysfunction compared to healthy controls (22,66,67,69, 70,74,80,84,85,88,89,96,97,99,100). Two studies showed that healthy populations demonstrated greater sexual dysfunction than their matched inflammatory arthritis populations (69,80). Demir et al (69) suggested that this result may be due to excluding psychiatric history and antidepressant use, which may have reduced the prevalence of mental health conditions and sexual dysfunction sequelae among the inflammatory arthritis group. However, 4 other studies used these exclusion criteria, and their inflammatory arthritis populations had greater sexual dysfunction than controls; no statistically significant difference in depression between the inflammatory arthritis group and healthy controls was observed (22,66,84,89). Hari et al (80) reported that healthy controls had lower FSFI mean scores than the inflammatory arthritis population, with both groups falling into the sexual dysfunction category, but the prevalence of sexual dysfunction was highest among the inflammatory arthritis group (76%) compared with healthy controls (47.5%).

Several studies used the IIEF as an outcome measure and showed mean scores of ≤25, indicating erectile dysfunction in inflammatory arthritis populations (62,65,79,88,90,116,117). Two studies showed that control group mean scores were on the threshold for erectile dysfunction, but these scores were not lower than the mean scores for patients with inflammatory arthritis (62,79). Bal et al (62) reported that these scores were not significantly different between groups, but due to a small sample size this study likely lacked adequate statistical power to observe a meaningful difference. While mean scores of the control group in the study by Dhakad et al (79) also suggested erectile dysfunction, IIEF mean scores of the inflammatory arthritis group were significantly lower. Erectile dysfunction has a multifactorial etiology, which may explain the prevalence of this condition among healthy controls (122,123). However, on a background of other disease-related impacts in men (such as pain, mobility restrictions, and fatigue), inflammatory arthritis appears to be consistently related to impaired sexual function and to be a key contributor to compromised intimate relationships.

The synthesized qualitative data support the quantitative findings, providing further evidence about the impact of inflammatory arthritis on sexual health and relationships. While clinical tools such as the FSFI and IIEF were useful in quantifying sexual dysfunction, data from the included qualitative studies provided more in-depth insights, particularly with respect to how intimate relationships were compromised. The reported impacts on intimate relationships differed across studies and samples, which may reflect the dynamics of individual relationships. For example, some participants reported a decreased focus on sexual intercourse, while others felt pressured to maintain intimate relationships despite their apparent sexual dysfunction (8,93). This variability may also reflect varying levels of partners' understanding of the sexual dysfunction associated with inflammatory arthritis. Partners with a greater understanding assisted to strengthen relationships, while among those who poorly understood disease impacts, tension and fear were created within relationships (8,75,93,118).

The strengths of this review included our comprehensive systematic review methods, which involved a specialist research librarian during search strategy development and the involvement of at least 2 independent reviewers at every stage of the review process. Unlike previous reviews (29–39), both sexes were considered, quantitative and qualitative study designs were included, and all types of inflammatory arthritis were included, whereas previous reviews were mostly disease-specific (6,28–34,36–51). This review also covered a broad range of geographic regions. Overall risk of bias for the qualitative studies was reasonably low, according to the CASP tool (102). The GRADE-CERQual evaluation provides moderate confidence that the review findings can be used to appropriately answer our research question.

We also acknowledge the review limitations. We were unable to conduct a meta-analysis, given heterogeneity of study populations and outcome measures, and some of the included quantitative studies were of poor methodologic quality. Overall, 74% of the quantitative studies were considered to have a moderate risk of bias, suggesting that further research is likely to have an impact on our confidence of these findings. Nonetheless, the included studies represent the contemporary evidence base and provide consistent evidence of an association between inflammatory arthritis and sexual dysfunction. While gray literature was not systematically searched, we are confident that the comprehensive nature of our search strategy identified the breadth of evidence relating to inflammatory arthritis and sexual function and intimacy. Given the consistency identified in quantitative and qualitative data, we do not expect that unpublished work would change our overall findings. We observed a limited range of outcome measures reported in quantitative studies, which may introduce an outcomes bias when interpreting the available evidence. Due to the small number of eligible qualitative studies, metasynthesis was limited because themes and subthemes were drawn from only 6 studies (8,75,78,87,93,118). Furthermore, most studies explored the impact on sexual function rather than on intimate relationships. Finally, from the data available, we are unable to speculate on the temporal nature of the association between disease and sexual dysfunction and compromised relationships (since most studies sampled individuals with a disease duration of inflammatory arthritis of ≥5 years) and whether age, disease duration, management approaches, or other health-related factors are likely to mediate the relationship. Such data limitations represent an important area for future research. Based on the volume and quality of evidence reviewed, potential biases associated with cross-sectional studies and the importance of the topic to patients, we suggest that the impact of the findings is moderate.

Our review identified the fact that many types of inflammatory arthritis have substantial impacts on sexual function and intimate relationships. These issues are sensitive in nature and commonly addressed poorly in clinical practice because they may be embarrassing for the clinician and/or the patient to raise (4,8,9,16,18,19,21–24,56). Our findings can be used to increase clinicians' awareness and thus encourage discussions with their patients from the early stages of management. While raising these issues in initial consultations may be difficult, given competing disease priorities and the need to establish rapport and active disease management, our findings suggest that sexual health and relationships are important components of overall health and should therefore be components of routine inflammatory arthritis management (125).

Sexual dysfunction is prevalent in female and male populations diagnosed with various forms of inflammatory arthritis. Sexual dysfunction in inflammatory arthritis is associated with pain, reduced sexual desire, erectile dysfunction, fatigue, and mobility restrictions. Because sexual health is an important component of well-being, raising clinician and patient awareness of sexual dysfunction associated with inflammatory arthritis could facilitate the provision of more holistic care.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Briggs had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Ackerman, Van Doornum, Briggs.
Acquisition of data. Restoux, Dasariraju, Romero.
Analysis and interpretation of data. Restoux, Dasariraju, Ackerman, Van Doornum, Briggs.

REFERENCES

1. World Health Organization. International classification of functioning, disability and health. Geneva: WHO Library Cataloguing-in-Publication Data; 2001. URL: http://psychiatr.ru/download/1313?view=name=CF_18.pdf.
2. Elst P, Sybesma T, van der Stadt RJ, Prins AP, Muller WH, den Butter A. Sexual problems in rheumatoid arthritis and ankylosing spondylitis. Arthritis Rheumatol 1984;27:217–20.
3. Lin M, Lu M, Livneh H, Lai N, Guo H, Tsai T. Factors associated with sexual dysfunction in Taiwanese females with rheumatoid arthritis. BMC Womens Health 2017;17:12.
4. Akkus Y, Nakas D, Kalyoncu U. Factors affecting the sexual satisfaction of patients with rheumatoid arthritis and ankylosing spondylitis. Sex Disabil 2010;28:223–32.
5. Kraaimaat FW, Bakker AH, Janssen E, Bijlsma JW. Intrusiveness of rheumatoid arthritis on sexuality in male and female patients living with a spouse. Arthritis Care Res (Hoboken) 1996;9:120–5.
6. Kurizky PS, Mota LM. Sexual dysfunction in patients with psoriasis and psoriatic arthritis: a systematic review. Rev Bras Reumatol Engl Ed 2012;52:943–8.
7. El Miedany Y, El Gaafary M, El Aroussy N, Youssef S, Ahmed I. Sexual dysfunction in rheumatoid arthritis patients: arthritis and beyond. Clin Rheumatol 2012;31:601–6.
8. Hill J, Bird H, Thorpe R. Effects of rheumatoid arthritis on sexual activity and relationships. Rheumatology (Oxford) 2003;42:280–6.
9. Majerovitz S, Revenson TA. Sexuality and rheumatic disease: the significance of gender. Arthritis Care Res (Hoboken) 1994;7:29–34.
10. Van Berlo WT, Vennix P, Rasker JJ, van Rijswijk MH, Taal E, Weijmar schulz WC, et al. Rheumatic diseases and sexuality: a review of the literature. Rheumatol Europe 1999;28:113–7.
11. Ostlund G, Björk M, Valtersson E, Sverker A. Intimate relationships as perceived by patients with early rheumatoid arthritis: a qualitative interview study (the Swedish Tira Study) [abstract]. Ann Rheum Dis 2014;73 Suppl 2:1220.
12. Matheson L, Harcourt D, Hewlett S. "Your whole life, your whole world, it changes": partners' experiences of living with rheumatoid arthritis. Musculoskeletal Care 2010;8:46–54.
13. Yoshino S, Uchida S. Sexual problems of women with rheumatoid arthritis. Arch Phys Med Rehabil 1981;62:122–3.
14. Blake DJ. Sexual disorders among patients with arthritis. Intern Med Rev (Wash D C) 1988;9:173–82.
15. Cohen M. Sexuality and the arthritic patient: how well are we doing? J Rheumatol 1987;14:403–4.
16. Abdel-Nasser A, Ali E. Determinants of sexual disability and dissatisfaction in female patients with rheumatoid arthritis. Clin Rheumatol 2006;25:822–30.
17. Blake DJ, Maisiak R, Alarcon GS, Holley HL, Brown S. Sexual quality of life of patients with arthritis compared to arthritis-free controls. J Rheumatol 1987;14:570–6.
18. Rkain H, Allali F, Jroundi I, Hajjaj-Hassouni N. Socioeconomic impact of rheumatoid arthritis in Morocco. Joint Bone Spine 2006;73:278–83.
19. Van Berlo WT, van de Wiel HB, Taal E, Rasker JJ, Weijmar Schultz WC, van Rijswijk MH. Sexual functioning of people with rheumatoid arthritis: a multicenter study. Clin Rheumatol 2007;26:30–8.
20. Briggs AM, Jordan JE, Ackerman IN, Van Doornum S. Establishing cross-discipline consensus on contraception, pregnancy and breast feeding-related educational messages and clinical practices to support women with rheumatoid arthritis: an Australian Delphi study. BMJ 2016;6:e012139.
21. Özgül A, Peker F, Taskaynatan MA, Tan AK, Dinçer K, Kalyon TA. Effect of ankylosing spondylitis on health-related quality of life and different aspects of social life in young patients. Clin Rheumatol 2006;25:168–74.
22. Sariyildiz MA, Batmaz I, Dilek B, Bozkurt M, Karakoc M, Çevik R, et al. The impact of ankylosing spondylitis on female sexual functions. Int J Impot Res 2013;25:104–8.
23. Zautra AJ, Hoffman JM, Matt KS, Yocum D, Potter PT, Castro WL, et al. An examination of individual differences in the relationship between interpersonal stress and disease activity among women with rheumatoid arthritis. Arthritis Care Res (Hoboken) 1998;11:271–9.
24. Ackerman IN, Jordan JE, Van Doornum S, Ricardo M, Briggs AM. Understanding the information needs of women with rheumatoid arthritis concerning pregnancy, post-natal care and early

parenting: a mixed-methods study. BMC Musculoskelet Disord 2015;16:194.

25. Baldursson H, Brattstrom H. Sexual difficulties and total hip replacement in rheumatoid arthritis. Scand J Rheumatol 1979;8:214–6.
26. Pouchot J, Le Parc JM, Queffelec L, Sichere P, Flinois A. Perceptions in 7700 patients with rheumatoid arthritis compared to their families and physicians. Joint Bone Spine 2007;74:622–6.
27. Josefsson KA, Gard G. Sexual health in patients with rheumatoid arthritis: experiences, needs and communication with health care professionals. Musculoskeletal Care 2012;10:76–89.
28. Molina-Leyva A, Jiménez-Moleón JJ, Naranjo-Sintes R, Ruiz-Carrascosa JC. Sexual dysfunction in psoriasis: a systematic review. J Eur Acad Dermatol Venereol 2015;29:649–55.
29. Areskoug-Josefsson K, Oberg U. A literature review of the sexual health of women with rheumatoid arthritis. Musculoskeletal Care 2009;7:219–26.
30. Al-Ezzi MY, Pathak N, Tappuni AR, Khan KS. Primary Sjögren's syndrome impact on smell, taste, sexuality and quality of life in female patients: a systematic review and meta-analysis. Mod Rheumatol 2017;27:623–9.
31. Fan D, Liu L, Ding N, Liu S, Hu Y, Cai G, et al. Male sexual dysfunction and ankylosing spondylitis: a systematic review and metaanalysis. J Rheumatol 2015;42:252–7.
32. Knafo R, Thombs BD, Jewett L, Hudson M, Wigley F, Haythornthwaite JA. (Not) talking about sex: a systematic comparison of sexual impairment in women with systemic sclerosis and other chronic disease samples. Rheumatology (Oxford) 2009;48:1300–3.
33. Lotfi MA, Varga J, Hirsch IH. Erectile dysfunction in systemic sclerosis. J Urology 1995;45:879–81.
34. Parke AL. Sjögren's syndrome: a women's health problem. J Rheumatol Suppl 2000;61:4–5.
35. Rosenbaum TY. Musculoskeletal pain and sexual function in women. J Sex Med 2010;7:645–53.
36. Vinet E, Pineau C, Gordon C, Clarke AE, Bernatsky S. Systemic lupus erythematosus in women: impact on family size. Arthritis Rheum 2008;59:1656–60.
37. Yin R, Xu B, Li L, Fu T, Zhang L, Zhang Q, et al. The impact of systemic lupus erythematosus on women's sexual functioning: a systematic review and meta-analysis. Medicine (Baltimore) 2017;96:e7162.
38. Zahedi Niaki O, Bernatsky S, Vinet E. Reproductive issues in males with SLE. Curr Treatm Opt Rheumatol 2017;3:173–80.
39. Zhang Q, Zhou C, Chen H, Zhao Q, Li L, Cui Y, et al. Rheumatoid arthritis is associated with negatively variable impacts on domains of female sexual function: evidence from a systematic review and meta-analysis. Psychol Health Med 2018;23:114–25.
40. Gossec L, Berenbaum F, Chauvin P, Lamiraud K, Russo-Marie F, Joubert JM, et al. Reporting of patient-perceived impact of rheumatoid arthritis and axial spondyloarthritis over 10 years: a systematic literature review. Rheumatology (Oxford) 2014;53:1274–81.
41. Gudu T, Kiltz U, de Wit M, Kvien TK, Gossec L. Mapping the effect of psoriatic arthritis using the International Classification of Functioning, Disability and Health. J Rheumatol 2017;44:193–200.
42. Hill J. The impact of rheumatoid arthritis on patients' sex lives. Nurs Times 2004;100:34–5.
43. Liu YF, Dong H, Chen Z, Wang Y, Tu SH. Impact of ankylosing spondylitis on sexual function: a systematic review and meta analysis. Exp Ther Med 2015;9:1501–7.
44. Nakayama A, Tunnicliffe DJ, Thakkar V, Singh-Grewal D, O'Neill S, Craig JC, et al. Patients' perspectives and experiences living with systemic sclerosis: a systematic review and thematic synthesis of qualitative studies. J Rheumatol 2016;43:1363–75.
45. Saad S, Behrendt AE. Scleroderma and sexuality. J Sex Med 1996;33:215–20.
46. Shah AA, Wigley FM. Often forgotten manifestations of systemic sclerosis. Rheum Dis Clin North Am 2008;34:221–38.
47. Sutanto B, Singh-Grewal D, McNeil HP, O'Neill S, Craig JC, Jones J, et al. Experiences and perspectives of adults living with systemic lupus erythematosus: thematic synthesis of qualitative studies. Arthritis Care Res (Hoboken) 2013;65:1752–65.
48. Taylor PC, Moore A, Vasilescu R, Alvir J, Tarallo M. A structured literature review of the burden of illness and unmet needs in patients with rheumatoid arthritis: a current perspective. Rheumatol Int 2016;36:685–95.
49. Tristano AG. Impact of rheumatoid arthritis on sexual function. World J Orthop 2014;5:107–11.
50. Tristano AG. The impact of rheumatic diseases on sexual function. Rheumatol Int 2009;29:853–60.
51. Zhao S, Li E, Wang J, Luo L, Luo J, Zhao Z. Rheumatoid arthritis and risk of sexual dysfunction: a systematic review and metaanalysis. J Rheumatol 2018;45:1375–82.
52. Østensen M. New insights into sexual functioning and fertility in rheumatic diseases. Best Pract Res Clin Rheumatol 2004;18:219–32.
53. Panush RS, Mihailescu GD, Gornisiewicz MT, Sutaria SH, Wallace DJ. Sex and arthritis. Bull Rheum Dis 2000;49:1–4.
54. Berg KH, Rohde G, Prøven A, Almås E, Benestad EE, Østensen M, et al. Exploring the relationship between demographic and disease-related variables and perceived effect of health status on sexual activity in patients with axial spondyloarthritis: associations found only with non-disease variables. Scand J Rheumatol 2017;46:461–7.
55. Chaigne B, Finckh A, Alpizar-Rodriguez D, Courvoisier D, Ribi C, Chizzolini C. Differential impact of systemic lupus erythematosus and rheumatoid arthritis on health-related quality of life. Qual Life Res 2017;26:1767–75.
56. Miedany Y, Gaafary M, Aroussy N, Youssef S, Ahmed I. Sexual dysfunction in rheumatoid arthritis patients: arthritis and beyond. Int J Rheum Dis 2012;31:601–6.
57. Josefsson KA, Gard G. Women's experiences of sexual health when living with rheumatoid arthritis: an explorative qualitative study. BMC Musculoskelet Disord 2010;11:240.
58. Seawell AH, Danoff-Burg S. Body image and sexuality in women with and without systemic lupus erythematosus. Sex Roles 2005;53:865–76.
59. Dincer U, Cakar E, Kiralp MZ, Dursun H. Assessment of sexual dysfunction in male patients with ankylosing spondylitis. Rheumatol Int 2007;27:561–6.
60. Healey EL, Haywood KL, Jordan KP, Garratt AM, Ryan S, Packham JC. Ankylosing spondylitis and its impact on sexual relationships. Rheumatology (Oxford) 2009;48:1378–81.
61. Impens AJ, Rothman J, Schiopu E, Cole JC, Dang J, Gendrano N, et al. Sexual activity and functioning in female scleroderma patients. Clin Exp Rheumatol. 2009;27 Suppl:38–43.
62. Bal S, Bal K, Turan Y, Deniz G, Gurgan A, Berkit IK, et al. Sexual functions in ankylosing spondylitis. Rheumatol Int 2011;31:889–94.
63. Ozkorumak E, Karkucak M, Civil F, Tiryaki A, Ozden G. Sexual function in male patients with ankylosing spondylitis. Int J Impot Res 2011;23:262–7.
64. Gallinaro AL, Akagawa LL, Otuzi MH, Sampaio-Barros PD, Goncalves CR. Sexual activity in ankylosing spondylitis. Rev Bras Reumatol Engl Ed 2012;52:887–91.
65. Rezvani A, Ok S, Demir SE. Assessment of sexual functions in male patients with ankylosing spondylitis compared with healthy controls. Arch Rheumatol 2012;27:233–40.
66. Aras H, Aras B, Icagasioglu A, Yumusakhuylu Y, Kemahli E, Haliloglu S, et al. Sexual dysfunction in women with rheumatoid arthritis. Med Glas (Zenica) 2013;10:327–31.

67. Bongi SM, Del Rosso A, Mikhaylova S, Baccini M, Cerinic MM. Sexual function in Italian women with systemic sclerosis is affected by disease-related and psychological concerns. J Rheumatol 2013;40:1697–705.
68. Daleboudt GM, Broadbent E, McQueen F, Kaptein AA. The impact of illness perceptions on sexual functioning in patients with systemic lupus erythematosus. J Psychosom Res 2013;74:260–4.
69. Demir SE, Rezvani A, Ok S. Assessment of sexual functions in female patients with ankylosing spondylitis compared with healthy controls. Rheumatol Int 2013;33:57–63.
70. Garcia Morales M, Callejas Rubio JI, Peralta-Ramirez MI, Henares Romero LJ, Rios Fernandez R, Camps Garcia MT, et al. Impaired sexual function in women with systemic lupus erythematosus: a cross-sectional study. Lupus 2013;22:987–95.
71. Rostom S, Mengat M, Mawani N, Jinane H, Bahiri R, Hajjaj-Hassouni N. Sexual activity in Moroccan men with ankylosing spondylitis. Rheumatol Int 2013;33:1469–74.
72. Aguiar R, Ambrosio C, Cunha I, Barcelos A. Sexuality in spondyloarthritis: the impact of the disease. Acta Reumatol Port 2014;39:152–7.
73. Coskun B, Coskun BN, Atis G, Ergenekon E, Dilek K. Evaluation of sexual function in women with rheumatoid arthritis. J Urology 2014;10:1081–7.
74. Frikha F, Masmoudi J, Saidi N, Bahloul Z. Sexual dysfunction in married women with systemic sclerosis. Pan Afr Med J 2014;17:82.
75. Oksel E, Gunduzoglu NC. Investigation of life experiences of women with scleroderma. Sex Disabil 2014;32:15–21.
76. Önem R, Çelik S, Öncü J, Tankaya O, Kolat U, Sungu Danişmant B, et al. Assessment of marital adjustment and sexuality in women with rheumatoid arthritis. Arch Rheumatol 2014;29:280–8.
77. Rosato E, Rossi C, Molinaro I, Digiulio MA, Trombetta AC, Marra AM, et al. Sexual distress, sexual dysfunction and relationship quality in women with systemic sclerosis: correlation with clinical variables. Int J Immunopathol Pharmacol 2014;27:279–85.
78. Bagcivan G, Cinar FI, Cinarb M, Oflaz F, Uzun S, Pay S. Living with pain in ankylosing spondylitis: a qualitative study. Contemp Nurse 2015;51:135–47.
79. Dhakad U, Singh BP, Das SK, Wakhlu A, Kumar P, Srivastava D, et al. Sexual dysfunctions and lower urinary tract symptoms in ankylosing spondylitis. Int J Rheum Dis 2015;18:866–72.
80. Hari A, Rostom S, Lahlou R, Bahiri R, Hajjaj-Hassouni N. Sexual function in Moroccan women with rheumatoid arthritis and its relationship with disease activity. Clin Rheumatol 2015;34:1047–51.
81. Östlund G, Björk M, Valtersson E, Sverker A. Lived experiences of sex life difficulties in men and women with early RA: the Swedish TIRA Project. Musculoskeletal Care 2015;13:248–57.
82. Saadat SH, Ramezani A, Ahmadi K. Sexual self-concept and general health in rheumatoid arthritis patients. Iran Red Crescent Med J 2015;17:e19005.
83. Abda E, Selim Z, Teleb S, Zaghira M, Fawzy M, Hamed S. Sexual function in females with rheumatoid arthritis: relationship with physical and psychosocial states. Arch Rheumatol 2016;31: 239–47.
84. Akkurt HE, Yilmaz H, Yilmaz S, Parlak L, Ordahan B, Salli A. Evaluation of sexual dysfunction in females with ankylosing spondylitis. Arch Rheumatol 2016;31:41–7.
85. Priori R, Minniti A, Derme M, Antonazzo B, Brancatisano F, Ghirini S, et al. Quality of sexual life in women with primary Sjögren syndrome. J Rheumatol 2015;42:1427–31.
86. Khnaba D, Rostom S, Lahlou R, Bahiri R, Abouqal R, Hajjaj-Hassouni N. Sexual dysfunction and its determinants in Moroccan women with rheumatoid arthritis. Pan Afr Med J 2016;24:16.
87. Pendeke TF, Williamson IR. "Half the Man I Was": exploring accounts of emasculation and estrangement amongst British men living with systemic lupus erythematosus. Int J Mens Health 2016;15:165–73.
88. Sanchez K, Denys P, Giuliano F, Palazzo C, Berezne A, Abid H, et al. Systemic sclerosis: sexual dysfunction and lower urinary tract symptoms in 73 patients. Presse Med 2016;45:e79–89.
89. Isik H, Isik M, Aynioglu O, Karcaaltincaba D, Sahbaz A, Beyazcicek T, et al. Are the women with Sjögren's syndrome satisfied with their sexual activity? Rev Bras Reumatol Engl Ed 2017;57:210–6.
90. Santana T, Skare T, Delboni VS, Simione J, Campos AP, Nisihara R. Erectile dysfunction in ankylosing spondylitis patients. Int Braz J Urol 2017;43:730–5.
91. Dorner TE, Berner C, Haider S, Grabovac I, Lamprecht T, Fenzl KH, et al. Sexual health in patients with rheumatoid arthritis and the association between physical fitness and sexual function: a cross-sectional study. Rheumatol Int 2018;38:1103–14.
92. Helland Y, Dagfinrud H, Kvien TK. Perceived influence of health status on sexual activity in RA patients: associations with demographic and disease-related variables. Scand J Rheumatol 2008;37:194–9.
93. Helland Y, Kjeken I, Steen E, Kvien TK, Hauge MI, Dagfinrud H. Rheumatic diseases and sexuality: disease impact and self-management strategies. Arthritis Care Res (Hoboken) . 2011;63:743–50.
94. Kobelt G, Texier-Richard B, Mimoun S, Woronoff AS, Bertholon DR, Perdriger A, et al. Rheumatoid arthritis and sexuality: a patient survey in France. BMC Musculoskelet Disord 2012;13:170.
95. Levis B, Burri A, Hudson M, Baron M, Thombs BD. Sexual activity and impairment in women with systemic sclerosis compared to women from a general population sample. PLoS One 2012;7:e52129.
96. Schouffoer AA, van der Marel J, Ter Kuile MM, Weijenborg PT, Voskuyl A, Vliet Vlieland CW, et al. Impaired sexual function in women with systemic sclerosis: a cross-sectional study. Arthritis Rheum 2009;61:1601–8.
97. Tseng JC, Lu LY, Hu JC, Wang LF, Yen LJ, Wu HC, et al. The impact of systemic lupus erythematosus on women's sexual functioning. J Sex Med 2011;8:3389–97.
98. Yilmaz H, Polat HA, Yilmaz SD, Erkin G, Kucuksen S, Salli A, et al. Evaluation of sexual dysfunction in women with rheumatoid arthritis: a controlled study. J Sex Med 2012;9:2664–70.
99. Ugurlu G, Erten S, Ugurlu M, Caykoylu A, Altunoğlu A. Sexual dysfunction in female patients with primary Sjögren's syndrome and effects of depression: cross-sectional study. Sex Disabil 2014;32:197–204.
100. Van Nimwegen JF, Arends S, van Zuiden GS, Vissink A, Kroese FG, Bootsma H. The impact of primary Sjögren's syndrome on female sexual function. Rheumatology (Oxford) 2015;54:1286–93.
101. Hoy D, Brooks P, Woolf A, Blyth F, March L, Bain C, et al. Assessing risk of bias in prevalence studies: modification of an existing tool and evidence of interrater agreement. J Clin Epidemiol 2012;65:934–9.
102. Critical Appraisal Skills Programme. CASP qualitative checklist. 2018. URL: https://casp-uk.net/casp-tools-checklists/.
103. Chou L, Shamdasani P, Briggs A, Cicuttini F, Sullivan K, Seneviwickrama K, et al. Systematic scoping review of patients' perceived needs of health services for osteoporosis. Osteoporos Int 2017;28:3077–98.
104. Chou L, Ranger TA, Peiris W, Cicuttini FM, Urquhart DM, Sullivan K, et al. Patients' perceived needs of health care providers for low back pain management: a systematic scoping review. Spine J 2018;18:691–711.
105. Chou L, Ellis L, Papandony M, Seneviwickrama K, Cicuttini F, Sullivan K, et al. Patients' perceived needs of osteoarthritis health information: a systematic scoping review. PLoS One 2018;13:e0195489.
106. Chou L, Cicuttini FM, Urquhart DM, Anthony SN, Sullivan K, Seneviwickrama M, et al. People with low back pain perceive

needs for non-biomedical services in workplace, financial, social and household domains: a systematic review. J Physiother 2018;64:74–83.

107. Segan JD, Briggs AM, Chou L, Connelly KL, Seneviwickrama M, Sullivan K, et al. Patient-perceived health service needs in inflammatory arthritis: a systematic scoping review. Semin Arthritis Rheum 2018;47:765–77.
108. Papandony MC, Chou L, Seneviwickrama M, Cicuttini FM, Lasserre K, Teichtahl AJ, et al. Patients' perceived health service needs for osteoarthritis (OA) care: a scoping systematic review. Osteoarthritis Cartilage 2017;25:1010–25.
109. Hannes K, Macaitis K. A move to more systematic and transparent approaches in qualitative evidence synthesis: update on a review of published papers. Qual Res 2012;12:402–42.
110. Thomas J, Harden A. Methods for the thematic synthesis of qualitative research in systematic reviews. BMC Med Res Methodol 2008;8:45.
111. Barnett-Page E, Thomas J. Methods for the synthesis of qualitative research: a critical review. BMC Med Res Methodol 2009;9:59.
112. Lewin S, Glenton C, Munthe-Kaas H, Carlsen B, Colvin CJ, Gülmezoglu M, et al. Using qualitative evidence in decision making for health and social interventions: an approach to assess confidence in findings from qualitative evidence syntheses (GRADE-CERQual). PLoS Med 2015;12:e1001895.
113. Bhadauria S, Moser DK, Clements PJ, Singh RR, Lachenbruch PA, Pitkin RM, et al. Genital tract abnormalities and female sexual function impairment in systemic sclerosis. Am J Obstet Gynecol 1995;172:580–7.
114. Druley JA, Stephens MA, Coyne JC. Emotional and physical intimacy in coping with lupus: women's dilemmas of disclosure and approach. Health Psychol Open 1997;16:506–14.
115. Foocharoen C, Tyndall A, Hachulla E, Rosato E, Allanore Y, Farge-Bancel D, et al. Erectile dysfunction is frequent in systemic sclerosis and associated with severe disease: a study of the EULAR Scleroderma Trial and Research (EUSTAR) group. Arthritis Res Ther 2012;R37.
116. Pirildar T, Muezzinoglu T, Pirildar S. Sexual function in ankylosing spondylitis: a study of 65 men. J Clin Urol 2004;171:1598–600.
117. Sariyildiz MA, Batmaz I, Dilek B, Inanir A, Bez Y, Tahtasiz M, et al. Relationship of the sexual functions with the clinical parameters, radiological scores and the quality of life in male patients with ankylosing spondylitis. Rheumatol Int 2013;33:623–9.
118. Ostlund G, Bjork M, Valtersson E, Sverker A. Lived experiences of sex life difficulties in men and women with early RA: the Swedish TIRA Project. Musculoskeletal Care 2015;13:248–57.
119. Rosen C, Brown J, Heiman S, Leiblum C, Meston R, Shabsigh D. The Female Sexual Function Index (FSFI): a multidimensional self-report instrument for the assessment of female sexual function. J Sex Marital Ther 2000;26:191–208.
120. Rosen RC, Cappelleri J, Smith M, Lipsky J, Peña B. Development and evaluation of an abridged, 5-item version of the International Index of Erectile Function (IIEF-5) as a diagnostic tool for erectile dysfunction. Int J Impot Res 2000;11:319–26.
121. Rosato E, Barbano B, Gigante A, Aversa A, Cianci R, Molinaro I, et al. Erectile dysfunction, endothelium dysfunction, and microvascular damage in patients with systemic sclerosis. J Sex Med 2013;10:1380–8.
122. Weber MF, Smith DP, O'Connell DL, Patel MI, de Souza PL, Sitas F, et al. Risk factors for erectile dysfunction in a cohort of 108 477 Australian men. Med J Aust 2013;199:107–11.
123. Litwin M, Nied R, Dhanani N. Health-related quality of life in men with erectile dysfunction. J Gen Intern Med 1998;13:159–66.
124. Ryan S, Dawes P, Mayer B. Does inflammatory arthritis affect sexuality? Br J Rheumatol 1996;35 Suppl:19.
125. Van Doornum S, Ackerman IA, Briggs AM. Sexual dysfunction: an often overlooked concern for people with inflammatory arthritis. Expert Rev Clin Immunol 2019;15:1235–7.

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BRIEF REPORT

Impact of Having Family History of Psoriasis or Psoriatic Arthritis on Psoriatic Disease

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Objective. Psoriatic arthritis (PsA) has a genetic background. Approximately 40% of patients with psoriasis or PsA have a family history of psoriasis or PsA, which may affect disease features. The aim of this study was to assess the effects of family history of psoriasis and PsA on disease phenotypes.

Methods. Data from 1,393 patients recruited in the longitudinal, multicenter Psoriatic Arthritis International Database were analyzed. The effects of family history of psoriasis and/or PsA on characteristics of psoriasis and PsA were investigated using logistic regression.

Results. A total of 444 patients (31.9%) had a family history of psoriasis and/or PsA. These patients were more frequently women, had earlier onset of psoriasis, more frequent nail disease, enthesitis, and deformities, and less frequently achieved minimal disease activity. Among 444 patients, 335 only had psoriasis in their family, 74 had PsA, and 35 patients were not certain about having PsA and psoriasis in their family, so they were excluded from further analysis. In the multivariate analysis, family history of psoriasis was associated with younger age at onset of psoriasis (odds ratio [OR] 0.976) and presence of enthesitis (OR 1.931), whereas family history of PsA was associated with lower risk of plaque psoriasis (OR 0.417) and higher risk of deformities (OR 2.557). Family history of PsA versus psoriasis showed increased risk of deformities (OR 2.143) and lower risk of plaque psoriasis (OR 0.324).

Conclusion. Family history of psoriasis and PsA impacts skin phenotypes, musculoskeletal features, and disease severity. The link between family history of psoriasis/PsA and pustular/plaque phenotypes may point to a different genetic background and pathogenic mechanisms in these subsets.

INTRODUCTION

Psoriasis and psoriatic arthritis (PsA) are multidimensional diseases with a strong genetic component. The genetic basis of psoriasis and PsA is recognized based on family aggregation studies, epidemiologic studies, association studies with human leucocyte antigens, genome-wide linkage scans, and candidate gene studies (1). According to population-based epidemiologic studies,

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SIGNIFICANCE & INNOVATIONS

- Psoriasis and psoriatic arthritis (PsA) are diseases that have strong genetic backgrounds. The role of genetics is not only important for the occurrence of the disease but also impacts the phenotype of the patients.
- To date, all studies that have investigated the effect of family history have combined psoriasis and PsA and examined the effect in combination as psoriatic disease.
- Family history of psoriasis and PsA has an impact on skin phenotypes, musculoskeletal features, and disease severity. Family history of PsA versus psoriasis has increased risk of deformities and lower risk of plaque psoriasis.
- The latter is especially of interest because there are well-demonstrated differences in the pathogenesis of plaque versus pustular psoriasis, and the link between family history of psoriasis/PsA and pustular/plaque phenotypes may point to a different genetic background and pathogenic mechanisms in these subsets.

approximately 40% of patients with psoriasis or PsA have a family history of either of these in first-degree relatives (FDRs) (2). Also, for patients with PsA, the recurrence risk ratio (RR) for PsA and psoriasis in FDRs is very high (RR 30–55 for PsA and 4–10 for psoriasis) (3).

Cases of familial versus sporadic PsA have some differences in terms of disease features, such as an earlier age at onset of psoriasis, more frequent nail involvement, and more severe disease in the case of a family history of PsA and/or psoriasis (2).

To the best of our knowledge, studies evaluating the effects of family history have always combined psoriasis and PsA, and the individual effects have not been studied. Because of the genetic differences between psoriasis and PsA as well as the differences between familial and sporadic cases, we hypothesized that family history of psoriasis versus PsA may lead to different disease phenotypes.

PATIENTS AND METHODS

Patient and data collection. The Psoriatic Arthritis International Database is a prospective, multicenter registry for PsA, which was initially developed in Turkey in 2014 and has had the participation of Canada since 2015. Ethics approval was obtained from the local ethics committees (Hacettepe University Ethics Board, Ankara [GO 14/578]; Ottawa Health Science Network Research Ethics Board, Ottawa [20160436-01H]), and all patients gave informed consent prior to data collection. Patients were consecutively registered to the registry with the aim of investigating real-life data using a web-based system (www.trials-network.org). PsA diagnosis was based on the clinical decision of a rheumatologist, and 86.9% of these patients fulfilled the criteria of the Classification of Psoriatic Arthritis Study Group (4) In this registry, demographics (sex, date of birth, education level, smoking status, weight, height, and calculated body mass index), psoriasis-related data (type, duration, initial site, and nail involvement), and PsA-related data were collected; the details of the collection having been extensively described before (5). Family history was investigated for psoriasis and PsA separately by asking patients the question, "As far as you know, does any member of your family have psoriasis/PsA?" If the answer was affirmative, the relationship of the affected family member with the patient was documented, again, separately for psoriasis and PsA.

Statistical analysis. Descriptive analyses were given using mean ± SD values for continuous variables and number (percentage) for categorical variables. Either the chi-square test or Fisher's exact test was used to analyze differences between categorical data, while Kruskal-Wallis and Mann-Whitney U tests were applied to test statistical differences between continuous data, as appropriate. We performed logistic regression to determine independent predictors that may be associated with family history of psoriasis or PsA. Plaque psoriasis, nail involvement, presence of enthesitis and joint deformity, age of onset of psoriasis, and sex were included in the final regression model. Due to missing data, minimal disease activity (MDA) could not be included in the final model to calculate MDA status for a large number of patients. SPSS, version 22.0, was used to conduct all statistical analyses.

RESULTS

Effect of family history of psoriasis and/or PsA on disease characteristics. Among 1,393 patients in the database (mean ± SD age 48 ± 13.1 years; 63.2% female), 444 patients (31.9%) had a family history of psoriasis or PsA. Patients with a positive family history were more frequently women, had an earlier age at onset of psoriasis, had more frequent nail disease, enthesitis, and presence of deformities, and less frequently achieved MDA (Table 1). On the other hand, no statistical differences were observed for other demographics, clinical characteristics (such as body mass index, arthritis pattern, and number of skin involvement sites), disease activity (measured with the Bath Ankylosing Spondylitis Disease Activity Index), and functional indexes (measured with the Bath Ankylosing Spondylitis Functional Index and Health Assessment Questionnaire). Among patients with a family history of psoriasis or PsA, 320 (72%) had FDRs who had been affected; the rest were second-degree relatives.

Disease characteristics according to family history of psoriasis or PsA. The majority of patients with family history had only psoriasis in their family (335 of 444), while 74 patients had a family history of PsA. A total of 35 patients were not certain about

Table 1. Demographic and clinical features of patients with PsA with or without FH*

	FH of psoriasis or PsA (n = 444)	No FH of psoriasis or PsA (n = 949)	*P*	FH of PsA (n = 74)	FH of only psoriasis (n = 335)	*P*
Age, mean ± SD years	48 ± 13.2	48 ± 13.0	0.536	49 ± 13.0	48 ± 13.2	0.370
Sex						0.412
Male	145/444 (32.7)	368/949 (38.8)	0.028†	28/74 (37.8)	106/335 (31.6)	
Female	299/444 (67.3)	581/949 (61.2)		46/74 (62.2)	229/335 (68.4)	
Age at psoriasis onset, mean ± SD years	29 ± 14.8	31 ± 14.9	0.007†	31.9 ± 14.8	28.1 ± 14.4	<0.001†
Age at PsA onset, mean ± SD years	39 ± 13.8	40 ± 13.1	0.450	41 ± 13.4	39 ± 13.6	0.162
BMI, mean ± SD kg/m^2	28.4 ± 5.5	28.0 ± 5.1	0.316	27.8 ± 4.7	28.7 ± 5.8	0.360
Time of psoriasis onset						0.100
Before PsA	348/435 (80.0)	704/937 (75.8)	0.083	50/71 (70.4)	268/329 (81.5)	
Synchronous	77/435 (17.7)	195/937 (20.8)		19/71 (29.6)	53/329 (16.1)	
After PsA	10/435 (2.3)	38/937 (4.1)		2/71 (2.8)	8/329 (2.4)	
Type of skin lesions						0.001†
Plaque psoriasis	221/294 (75.2)	481/665 (72.3)	0.043†	30/52 (57.7)	183/231 (79.6)	
Pustular psoriasis	48/294 (16.3)	147/665 (22.1)		18/52 (34.6)	29/231 (12.6)	
Others	25/294 (8.5)	37/665 (5.6)		4/52 (7.7)	19/231 (8.2)	
No. of skin involvement sites						0.836
<3	287/376 (76.3)	576/773 (74.5)	0.504	49/64 (76.6)	223/296 (75.3)	
≥3	89/376 (23.7)	197/773 (25.5)		15/94 (23.4)	73/296 (24.7)	
Arthritis pattern						
Polyarthritis	186/442 (42.1)	393/945 (41.6)	0.862	37/74 (50.0)	136/334 (40.7)	0.144
Oligoarthritis	169/442 (38.2)	338/945 (35.8)	0.374	23/74 (31.1)	130/334 (39.5)	0.176
Monoarticular	17/442 (3.8)	40/945 (4.2)	0.738	4/74 (5.4)	13/334 (3.9)	0.566
DIP	78/442 (17.6)	165/945 (17.5)	0.932	14/74 (18.9)	58/334 (17.4)	0.751
Arthritis mutilans	2/442 (0.5)	7/945 (0.7)	0.533	0	2/334 (0.6)	0.505
Axial involvement	162/442 (36.7)	330/945 (34.9)	0.530	37/74 (50.0)	136/334 (40.7)	0.108
Joint deformity	86/332 (25.9)	126/632 (19.9)	0.034†	19/55 (34.5)	60/249 (24.1)	0.174
Dactylitis (ever)	132/443 (29.8)	281/948 (29.6)	0.953	19/74 (25.7)	105/334 (31.4)	0.330
Enthesitis (ever)	118/418 (28.2)	156/883 (17.7)	<0.001†	17/71 (23.9)	83/311 (26.7)	0.617
Nail involvement	225/443 (50.7)	281/948 (29.6)	0.032†	38/74 (51.4)	174/334 (52.1)	0.908
MDA	39/101 (38.6)	106/214 (49.5)	0.045†	8/17 (47.1)	28/77 (36.4)	0.412
BASFI, mean ± SD	2.9 ± 2.4	3.1 ± 2.4	0.626	2.9 ± 2.3	2.9 ± 2.3	0.952
BASDAI, mean ± SD	4.2 ± 2.4	3.9 ± 2.5	0.191	4.3 ± 2.2	4.1 ± 2.1	0.598
HAQ, mean ± SD	0.76 ± 0.7	0.71 ± 0.6	0.538	0.88 ± 0.7	0.72 ± 0.7	0.144
RF positivity	55/443 (12.4)	129/948 (13.6)	0.610	11/74 (14.9)	41/334 (12.3)	0.546

* Values are no./total no. (%) unless indicated otherwise. PsA = psoriatic arthritis; FH = family history; BMI = body mass index; DIP = distal interphalangeal; MDA = minimal disease activity; BASFI = Bath Ankylosing Spondylitis Functional Index; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; HAQ = Health Assessment Questionnaire; RF = rheumatoid factor.
† Significant.

having PsA in addition to psoriasis in their family and therefore were excluded from further analysis. The onset of psoriasis occurred earlier in patients with a family history of psoriasis compared to those with a family history of PsA (mean ± SD age 28.1 ± 14.4 years versus 31.9 ± 14.8 years; $P < 0.001$) (Table 1).

There were differences in the type of skin lesions according to family history of psoriasis or PsA. Plaque psoriasis was more common in family history of psoriasis, while there was an increased frequency of pustular psoriasis in family history of PsA (Figure 1).

Univariate analysis of the effect of family history on disease characteristics. In comparison to patients with no family history, having a family member with psoriasis was a risk factor for nail disease, enthesitis, plaque psoriasis, and younger age of onset of psoriasis. Also, women had more family history of psoriasis (Table 2).

Similarly, when compared to patients with no family history, having a family member with PsA was a risk factor for the presence of deformities and protective against having plaque

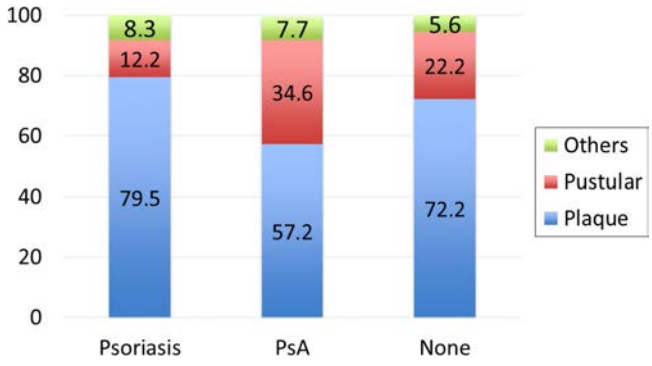

Figure 1. Distribution of skin lesions according to family history. Numbers are given as percentages. PsA = psoriatic arthritis.

Table 2. Univariate and multivariate analysis in patients with family history of psoriasis or PsA*

	Psoriasis vs. none, univariate		Psoriasis vs. none, multivariate†		PsA vs. none, univariate		PsA vs. none, multivariate‡		PsA vs. psoriasis, univariate		PsA vs. psoriasis, multivariate§	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Age at psoriasis onset, years	0.985 (0.976–0.994)	0.001¶	0.976 (0.964–0.989)	<0.001¶	1.002 (0.986–1.019)	0.763	0.995 (0.973–1.018)	0.670	1.018 (1.000–1.036)	0.046¶	1.022 (0.997–1.047)	0.085
Sex	1.317 (1.052–1.786)	0.020¶	1.213 (0.828–1.777)	0.321	1.042 (0.640–1.697)	0.868	0.814 (0.420–1.575)	0.541	1.315 (0.779–2.219)	0.305	0.636 (0.304–1.330)	0.636
Nail involvement (ever)	1.353 (1.054–1.737)	0.018¶	0.989 (0.678–1.442)	0.952	1.313 (0.818–2.109)	0.259	1.329 (0.679–2.602)	0.406	0.971 (0.586–1.606)	0.908	1.252 (0.597–2.627)	0.552
Enthesitis (ever)	1.709 (1.261–2.317)	0.001¶	1.931 (1.276–2.922)	0.002¶	1.467 (0.828–2.599)	0.189	0.832 (0.361–1.917)	0.665	0.858 (0.471–1.563)	0.617	0.421 (0.173–1.025)	0.057
Presence of deformities	0.784 (0.553–1.113)	0.174	1.293 (0.819–2.041)	0.269	1.926 (1.093–3.501)	0.024¶	2.557 (1.250–5.234)	0.010¶	1.535 (0.825–2.854)	0.176	2.143 (1.052–5.367)	0.037¶
Plaque psoriasis	1.461 (1.019–2.096)	0.039¶	1.399 (0.884–2.214)	0.151	0.523 (0.294–0.930)	0.027¶	0.417 (0.213–0.816)	0.011¶	0.358 (0.189–0.675)	0.002¶	0.324 (0.152–0.694)	0.004¶

* PsA = psoriatic arthritis; OR = odds ratio; 95% CI = 95% confidence interval.
† N = 603.
‡ N = 473.
§ N = 212.
¶ Significant.

psoriasis (Table 2). Family history of PsA versus psoriasis was a risk factor for plaque psoriasis. This group also had psoriasis at an older age.

Multivariate analysis of the effect of family history on disease characteristics. In the multivariate analysis, in comparison to patients with no family history, having a family member with psoriasis remained a risk factor for enthesitis and younger age at onset of psoriasis (Table 2). For the comparison of family history of PsA versus none, the same factors that were identified in the univariate analysis remained to be significant in the multivariate analysis. Having a family member with PsA was a risk factor for the presence of deformities and protective against having plaque psoriasis (Table 2). Family history of PsA versus family history of psoriasis had increased risk for deformities and lower risk for plaque psoriasis.

The effect of paternal versus maternal transmission. Because previous studies have demonstrated a difference between paternal versus maternal transmission (6), further analysis was made to test a similar effect in our registry. A total of 174 patients had an affected parent (psoriasis or PsA). A total of 92 of these patients (53%) had an affected father; 82 patients (47%) had an affected mother. There was no difference in disease characteristics among patients whose father or mother was affected (data not shown).

DISCUSSION

The genetic load of psoriasis and PsA has been well described in the literature, as has the effect of family history of psoriasis and/or PsA on disease outcomes (2,3,6,7). However, the differences between psoriasis and PsA in family history have not been examined before. To the best of our knowledge, this is the first study that has shown that having family member(s) with PsA versus psoriasis has an impact on the disease phenotype and severity, with patients who have a family history of PsA having an increased risk of pustular psoriasis and more deformities compared to a family history of psoriasis.

A large number of genetic loci have been described in psoriasis in the last decade by the genome-wide association studies. Fewer studies have been conducted to identify PsA risk variants (7–11). The studies show that the significant differences in the genetic architecture of psoriasis and PsA may also be reflected in the phenotypic characteristics of these diseases. Differences in the strength of association with psoriasis and PsA have been repeatedly observed for the major histocompatibility complex, including a stronger association of HLA–C*06 with psoriasis and a stronger association of HLA–B*27 with PsA. Two other important PsA risk variants resulting from these studies are near *IL23R* and near *TNFAIP3* (10–13). Our data confirm that the genetic differences between psoriasis and PsA in the family may cause a different phenotype in the index patient. The histologic and clinical differences between plague and pustular psoriasis may also be due to the genetic differences between patients (14). Innate immune system abnormalities have been shown to be important in pustular psoriasis, with an increased role of interleukin-1 and interleukin-36 in the pathogenesis (15). Paradoxical psoriasis in patients treated with anti–tumor necrosis factor also quite frequently appears to be pustular psoriasis, suggesting a different pathogenic mechanism (16). The simple difference in PsA versus psoriasis in family members may point to a deeper genetic difference in familial cases of psoriatic disease and may be an important factor to consider in the era of personalized medicine.

The literature supports some clinical differences between familial and sporadic cases of PsA, such as an earlier age of onset of psoriasis, more frequent nail involvement, more severe disease, higher frequency of skin lesions prior to arthritis, higher erythrocyte sedimentation rate, and a lower incidence of rheumatoid factor positivity (2,3,6). Similarly, in this cohort we found an earlier age of onset of psoriasis, more frequent nail involvement, more frequent enthesitis, and more frequent deformity in familial cases, which is evidence for the external validity of our cohort and data collection.

Our study has some limitations. Family history is not always easy to obtain because patients may or may not be aware of diseases of their family members, especially for second-degree relatives or if family members have a mild disease. However, this is true for all studies that investigate family history, and the accuracy of this method has been demonstrated previously (17). Family history of psoriasis or PsA was found in 31.9% of the patients in our study, which confirms external validity and is in agreement with the literature (2). Our data are only based on observations, and lack of genetic analysis in the patients prevents us from drawing firm conclusions. Also, the data were collected in 35 centers, and there may be variations on data collection across centers despite the precautions to enhance homogeneity taken prior the study.

In conclusion, family history of psoriasis and PsA has an impact on skin phenotypes, musculoskeletal features, and disease severity. The link between family history of psoriasis/PsA and pustular/plaque phenotypes may point to a different genetic background and pathogenic mechanisms in these subsets.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version

to be submitted for publication. Dr. Aydin had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Solmaz, Bakirci, Kimyon, Gunal, Dogru, Bayindir, Dalkilic, Ozisler, Can, Akar, Cetin, Kilic, Tarhan, Kucuksahin, Omma, Gonullu, Yildiz, Ersozlu, Cinar, Al-Onazi, Erden, Tufan, Yilmaz, Pehlevan, Kalyoncu, Aydin.

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Analysis and interpretation of data. Solmaz, Bakirci, Ozisler, Akar, Yavuz, Kalyoncu, Aydin.

REFERENCES

1. Rahman P, Elder JT. Genetic epidemiology of psoriasis and psoriatic arthritis. Ann Rheum Dis 2005;64:37–39.
2. Rahman P, Schentag CT, Beaton M, Gladman DD. Comparison of clinical and immunogenetic features in familial versus sporadic psoriatic arthritis. Clin Exp Rheumatol 2000;18:7–12.
3. Chandran V, Schentag CT, Brockbank JE, Pellett FJ, Shanmugarajah S, Toloza SM, et al. Familial aggregation of psoriatic arthritis. Ann Rheum Dis 2009;68:664–7.
4. Taylor W, Gladman D, Helliwell P, Marchesoni A, Mease P, Mielants H, and the CASPAR Study Group. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. Arthritis Rheum 2006;54:2665–73.
5. Kalyoncu U, Bayindir Ö, Öksüz MF, Doğru A, Kimyon G, Tarhan EF, et al. The Psoriatic Arthritis Registry of Turkey: results of a multicentre registry on 1081 patients. Rheumatology (Oxford) 2017;56:279–86.
6. Rahman P, Gladman DD, Schentag CT, Petronis A. Excessive paternal transmission in psoriatic arthritis. Arthritis Rheum 1999;42:1228–31.
7. Myers A, Kay LJ, Lynch SA, Walker DJ. Recurrence risk for psoriasis and psoriatic arthritis within sibships. Rheumatology (Oxford) 2005;44:773–6.
8. Stuart PE, Nair RP, Tsoi LC, Tejasvi T, Das S, Kang HM, et al. Genome-wide association analysis of psoriatic arthritis and cutaneous psoriasis reveals differences in their genetic architecture. Am J Hum Genet 2015;97:816–36.
9. Lønnberg AS, Skov L, Skytthe A, Kyvik KO, Pedersen OB, Thomsen SF. Heritability of psoriasis in a large twin sample. Br J Dermatol 2013;169:412–16.
10. Liu Y, Helms C, Liao W, Zaba LC, Duan S, Gardner J, et al. A genome-wide association study of psoriasis and psoriatic arthritis identifies new disease loci. PLoS Genet 2008;4:e1000041.
11. Scarpa R, Cosentini E, Manguso F, Oriente A, Peluso R, Atteno M, et al. Clinical and genetic aspects of psoriatic arthritis "sine psoriasis." J Rheumatol 2003;30:2638–40.
12. Hüffmeier U, Uebe S, Ekici AB, Bowes J, Giardina E, Korendowych E, et al. Common variants at TRAF3IP2 are associated with susceptibility to psoriatic arthritis and psoriasis. Nat Genet 2011;42:996–9.
13. Ellinghaus E, Stuart PE, Ellinghaus D, Nair RP, Debrus S, Raelson JV, et al. Genome-wide meta-analysis of psoriatic arthritis identifies susceptibility locus at REL. J Invest Dermatol 2012;132:1133–40.
14. Mansouri B, Benjegerdes K, Hyde K, Kivelevitch D. Pustular psoriasis: pathophysiology and current treatment perspectives. Psoriasis (Auckl) 2016;6:131–44.
15. Johnston A, Xing X, Wolterink L, Barnes DH, Yin ZQ, Reingold L, et al. IL-1 and IL-36 are dominant cytokines in generalized pustular psoriasis. J Allergy Clin Immunol 2017;140:109–20.
16. Ciccarelli F, de Martinis M, Sirufo MM, Ginaldi L. Psoriasis induced by anti-tumor necrosis factor alpha agents: a comprehensive review of the literature. Acta Dermatovenerologica Croat 2016;24:169–74.
17. Rahman P, Beaton M, Schentag CT, Gladman DD. Accuracy of self-reported family history in psoriatic arthritis. J Rheumatol 2000;27:824–5.

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"Reluctant to Assess Pain": A Qualitative Study of Health Care Professionals' Beliefs About the Role of Pain in Juvenile Idiopathic Arthritis

Rebecca Rachael Lee,[1] Amir Rashid,[1] Wendy Thomson,[2] and Lis Cordingley[2]

Objective. Reducing pain is one of the main health priorities for children and young people with juvenile idiopathic arthritis (JIA); however, some studies indicate that pain is not routinely assessed in this patient group. The aim of this study was to explore health care professionals' (HCPs) beliefs about the role of pain and the prioritization of its assessment in children and young people with JIA.

Methods. Semi-structured interviews were conducted with HCPs who manage children and young people with JIA in the UK (including consultant and trainee pediatric rheumatologists, nurses, physical therapists, and occupational therapists). Data were analyzed qualitatively following a framework analysis approach.

Results. Twenty-one HCPs participated. Analyses of the data identified 6 themes, including lack of training and low confidence in pain assessment, reluctance to engage in pain discussions, low prioritization of pain assessment, specific beliefs about the nature of pain in JIA, treatment of pain in JIA, and undervaluing pain reports. Assessment of pain symptoms was regarded as a low priority and some HCPs actively avoided conversations about pain.

Conclusion. These findings indicate that the assessment of pain in children and young people with JIA may be limited by knowledge, skills, and attitudinal factors. HCPs' accounts of their beliefs about pain in JIA and their low prioritization of pain in clinical practice suggest that a shift in perceptions about pain management may be helpful for professionals managing children and young people with this condition.

INTRODUCTION

Juvenile idiopathic arthritis (JIA) is a chronic inflammatory arthritis diagnosed in children and young people <16 years of age (1). Chronic pain is one of the most common features of this long-term condition (2–6) and many studies have demonstrated that pain has a high daily prevalence in JIA (7,8). Managing JIA-related pain can be both a challenge and a burden for children and young people, as it can interfere with multiple aspects of everyday life (9) including physical, social, and academic activities (10).

In a thematic synthesis of the experiences of children and young people living with JIA, Tong et al (11) found that the invisible nature of pain was described as the "worst thing" about living with the condition. In another study, patients viewed opportunities to describe the course of pain in JIA as high priority, whereas health care professionals' (HCPs') views did not correspond (12). Some authors suggest that HCPs regularly overlook the assessment of pain in children with long-term conditions (13,14), however it is not clear why this might be the case. This situation is problematic because the presence of pain in children with JIA is not fully explained by disease activity alone (2,15). Chronic pain continues to be a burden even throughout periods when underlying disease processes are controlled with medication and disease activity is low (5,7,16–19). Furthermore, HCPs have been poor at predicting levels of pain in children with JIA, sometimes providing overestimated (i.e., worse) ratings than children themselves (20) and sometimes underestimations (21). The nonlinear relationship between pain and disease activity, taken together with HCPs inability to accurately estimate pain levels, suggests that a separate assessment of pain is necessary and should include self-report of pain symptoms by children.

The views expressed herein are those of the authors and not necessarily those of the National Health Service, the National Institute for Health Research, or the UK Department of Health.

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SIGNIFICANCE & INNOVATIONS

- Health care professionals reported gaps in pain-specific knowledge and skills to assess and manage pain in children with juvenile idiopathic arthritis (JIA).
- Beliefs about the occurrence of pain in the context of JIA contributed to a reluctance to prioritize pain assessment by some rheumatologists, nurses, physical therapists and occupational therapists.
- Therapists were more likely than rheumatologists to express concerns about an "over-medicalized" approach to treatment of JIA.
- A paradigm shift in approaches to pain assessment and communication by professionals managing those with JIA may be useful to improve both pain management and pain communication with patients and families.

Pain assessment provides the basis upon which to develop, refine, and evaluate pain management strategies and is necessary to achieve improvements in pain symptoms (22). A full pain assessment requires attention to intensity, frequency, location, and interference, information which should inform JIA care decisions (10). Despite many authors advocating thorough pain assessment in JIA, there is little published literature investigating HCPs attention to pain in this long-term condition. The aim of the current research study was to explore HCPs' beliefs about the role of pain and the prioritization of its assessment in professionals involved in the management of children and young people with JIA throughout the UK.

MATERIALS AND METHODS

The research that was carried out was in compliance with the Helsinki Declaration. Ethical approval was granted by the authors' institutional research ethics committee (ref: 15454). HCPs were recruited via a study advertisement circulated by The British Society for Paediatric and Adolescent Rheumatology, a professional membership organization (23). HCPs were eligible for the study if they worked in the UK National Health Service as pediatric rheumatologists (either consultant or trainee), pediatricians, nurse specialists, physical therapists, or occupational therapists managing children and young people with JIA.

A data-driven inductive approach was chosen to guide data collection and analysis as there was no predefined theory about pain assessment and communication in UK pediatric rheumatology settings. Interviews were conducted either face-to-face or over the telephone and all were digitally audio recorded. Interviews were semistructured and followed the format and questions outlined in the interview topic guide (Table 1). The first draft of the interview topic guide was developed among the authors, mainly using observations of clinical consultations between pediatric rheumatologists and patients with JIA. During the observations of HCPs in the clinic of 1 author (RRL), notes were made about issues discussed with patients, explanations of disease or pain, attention given to assessment, and specific advice given about treatment. These observations were mapped onto existing rheumatology and pain-specific literature (including research and clinical guidelines) about pain assessment and management issues in each field. Contrasts in the pain assessment approaches in the fields of pain and rheumatology were used to highlight specific problems. Issues and problems raised through observations and research articles were then developed into questions by the study team.

The interview topic guide was refined after piloting with a trainee pediatric rheumatologist. Audio recordings of interviews were transcribed verbatim. All audio recorded interviews were uploaded to and analyzed in NVivo 10 (QSR International).

The framework analysis method (24) was adopted. The 5 stages of conducting framework analysis include familiarization, identification of a thematic framework, indexing, charting, and mapping/interpretation. One author (RRL), an experienced qualitative analyst with a research background in Health Psychology, served as the main analyst and coded all of the data in NVivo using audio recordings and interview transcripts simultaneously. Data collection was paused after the first 6 interviews as a familiarization exercise for the main data analyst, to ensure the data being captured was in line with the aims of the study and so that the interview guide could be modified if the data collected was not appropriate. Two other members of the research team (AR and LC) reviewed audio recordings, transcripts, initial themes, and interpretations produced from the main data analyst at this stage of the analysis. Disagreements (e.g., the meaning of participant quotations and how they mapped onto themes in the initial index) were addressed through group discussions until clarity and consensus were obtained. The interview guide was not modified following this because questions were considered to be appropriate and data capture was relevant to the aims of the study (as agreed upon by all authors).

During this data collection pause, an initial index of themes was developed in line with the framework analysis approach (24) by the main data analyst. The initial index portrayed a priori issues (reflecting the research aims and questions posed in the interview guide) as well as new issues raised by participants and recurring patterns of views in data. The initial index included categories of early emerging themes and was used to examine, sort, and guide the interpretation of interview data. The initial index was refined and developed further as the remaining interview data were collected and interpreted. New themes were added to the initial index, and the interpretations of initial themes were adapted based upon new evidence. The process of refining and developing the initial index was conducted with 2 other members of the research team (AR and LC) until a thorough index that could be applied to participant

Table 1. Final topic guide used in semistructured interviews*

Questions	Probes and prompts
What is your experience of working with individuals with JIA?	Current role and past roles? Frequency of contact with patients with JIA? Training in assessment and management of JIA/pain?
How/what do you consider the role of pain to be in JIA?	What is the importance of pain for CYP with JIA? What is the relationship of pain with disease activity?
What do you think are the main influences/causes upon the amount/severity of pain an individual with JIA suffers from?	What are the biomedical influences? What are the biopsychosocial influences?
Do you believe that significant attention to pain is given in clinical consultations between health care professionals and CYP with JIA?	Could you tell me about some of your own experiences of addressing pain in these patients? Can you tell me about any possible reasons or scenarios in which pain is/is not significant to consider?
Do you routinely assess pain as part of your clinical appointments with patients?	What do you tend to focus on? What do you tend to not spend much time covering?
How do you communicate with patients with JIA about pain symptoms?	How is the topic of pain approached? Are there any particular barriers to talking about pain? What helps you and patients to communicate about pain? Do you use any particular scales? Do you think the reporter of pain is important? Are there any facets of pain information which you find to be more important than others (e.g., information about intensity, location, frequency)?
To what extent do you think information about pain is used to guide management/treatment decisions in JIA?	How does pain information affect your treatment/management decisions? What would you adapt in your treatment/management plan of patients based on pain reports?
What advice do you give patients about pain management?	What advice do you give regarding the impact of pain? What advice do you give if patients complain of their joints being painful?
To what extent do you think pain assessment is conducted in current practice?	What issues do you envisage with aiming to make pain assessment better in practice?
Do you use any particular guidelines or policy documents for measuring progress in JIA?	What guidelines are you aware of? What is your opinion on the appropriateness/inappropriateness of outcomes measured?
How do you think we can make pain assessment better for CYP with JIA?	Do you think any particular tools would be helpful? Or any particular resources helpful? Do you think particular teams of professionals are helpful to have involved in assessment and pain management?
Do you think pain assessment is conducted similarly between all groups of health care professionals?	Do you think different professional teams are better placed to assess pain? Do you think there is a difference in pain assessment approaches between people working in the same profession?

* JIA = juvenile idiopathic arthritis; CYP = children and young people.

data was created (see Supplementary Table 1, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23827/abstract).

Using the index, data were arranged hierarchically into themes and subthemes by the main analyst (RRL). A matrix output was generated once all interview transcripts had been organized into these themes/nodes (25). Comparisons were made between participants' accounts to look for meaning and connections. These connections were then organized, grouped, and mapped using the index and were then interpreted into overarching themes and narratives. Two other members of the research team (AR and LC) reviewed the organized data, emerging themes, and narratives for clarity and meaningfulness. Themes were reorganized and reinterpreted as part of some discussions between the research team. When there were any apparent gaps in the themes identified, interview transcripts were revisited for additional coding to support and/or refute the interpretations generated from the data.

After 15 interviews, the materialization of new information from participants plateaued. Six planned interviews were

Table 2. Participant characteristics

Health care profession	Experience, years (range)	Interview type		Sex		Total no. of participants
		Telephone	Face-to-face	Female	Male	
Pediatric rheumatologists*	1.5–20	6	2	7	1	8
Pediatricians	2	0	1	1	0	1
Nurses	1–5	3	0	3	0	3
Physical therapists	0.5–12	3	3	5	1	6
Occupational therapists	0.25–14	3	0	3	0	3

* Including 2 trainees.

carried out to ensure that data saturation had occurred. Despite ongoing interest from 5 professionals, no further interviews were planned.

RESULTS

Participant demographics. Twenty-one HCPs participated, working in 12 different pediatric rheumatology departments across England and the Republic of Ireland (Table 2). Interview times ranged from 28 to 65 minutes (mean = 45 minutes). The sample of HCPs included 19 female and 2 male, which is representative of rheumatology departments in the UK (latest estimates indicate 94% of staff are female) (26). Six interviews were conducted face-to-face and 15 interviews were completed over the telephone.

Themes and interpretation. Six overarching themes were identified: 1) training, confidence, and competencies in pain assessment; 2) reluctance to engage in pain discussions; 3) low prioritization of pain assessment; 4) beliefs about pain in JIA; 5) treatment of pain; and 6) undervaluing pain reports. Each of these themes will be discussed as a narrative account in subsequent tables.

Theme 1: Training, confidence, and competencies in pain assessment (Table 3). Participants reported that they had had little or no training on how to assess chronic pain symptoms in children and young people with JIA, and that pain was not an explicit part of rheumatology training. Pain education may have occurred as part of general medical training under the premise that additional knowledge and skills would be picked up in practice by individuals specializing in the field of pediatric rheumatology. Participants indicated that they only learned how to assess and manage pain symptoms in JIA by following current departmental practices. Participants perceived a lack of availability of pain-specific knowledge or skills training at later stages of their careers.

Participants reported their low levels of confidence in approaching and talking to children and young people about pain experiences because of their lack of pain training. Some felt that other HCP groups were more equipped for this task or perceived other HCPs as having the specific competencies needed for assessing pain in this group. An issue that recurred in several interviews was the idea that therapists, such as occupational or physical therapists, were best placed for assessing pain. Rheumatologists generally discounted themselves as being the best placed for assessing pain because they did not know how to ask the right questions about pain and were not trained to do so. In the accounts provided by therapists, their perceived suitability was linked to the additional time available, less formal consultations and more regular contact with patients, as well as their specific skill sets relating to pain assessment. Therapists believed that referrals that they received to manage patients with pain could sometimes be due to rheumatologists not having the skill set required to address pain without therapy input. Although therapists discussed being best placed to assess pain, it transpired in later themes that there were several other factors that appear to contribute to the lack of pain assessment by allied health professionals.

Theme 2: Reluctance to engage in pain discussions (Table 3). A reluctance to directly elicit information from patients about their pain was found in some of the interviews conducted. Some participants indicated that explicit assessment was not necessary in order to assess pain levels of individuals with JIA. Rather, participants in the current study believed that they could make sense of pain of a child or young person by how they reported on other aspects of their condition, such as joint stiffness. Here, participants felt able to make judgments about pain levels without direct reports from their patients.

Another reason why participants did not ask about pain was because some HCPs feared that there would be undesirable consequences of doing so. There were some concerns that patients may exaggerate or misrepresent their pain experiences simply because they were being asked about pain, or because by putting pain assessment on the agenda patients would feel obliged to report it. Furthermore, participants thought that discussions about pain or a focus on symptoms may lead to children and young people feeling more pain as a consequence of the consultation. Finally, participants discussed how conversations about pain were by their nature "depressing" and could possibly worsen well-being or lower patient motivation for self-management.

HCPs rarely asked for pain information from patients directly in clinical consultations, which (as discussed) demonstrates a reluctance to approach and seek information about pain from a HCPs perspective; however, a notable finding in the current study is that even when patients themselves brought up the topic of pain in consultations, some HCPs would actively avoid engaging in conversations. Some participants reported that they would purposefully not become involved in discussions about pain because they were aware that they did not have the resources to address pain management. The difficulties associated with addressing the root cause of pain acted as a deterrent to approaching the subject.

Theme 3: Low prioritization of pain assessment (Table 4). This theme is closely related to the previous theme but shows how a reluctance to discuss pain can contribute to the low prioritization of the assessment of pain across the range of HCPs interviewed. Participants reported that they did not want to dwell on pain in clinical consultations and that pain assessment was not necessary at every rheumatology appointment.

Some participants acknowledged the importance of pain assessment but that it had a lower priority relative to other

Table 3. Themes 1 and 2, subthemes, and associated interview excerpts*

Themes and subthemes	Interview excerpts
Theme 1: Training, confidence, and competencies in pain assessment	
Subthemes	
There is little/no formal training in how to assess chronic pain. Pain education may occur in medical school but these skills are forgotten about in later training stages.	"No, I haven't had particular pain teaching. We probably did in medical school, but I can't really remember" (Participant 3, pediatrician). "I don't think anyone has very good pain training. I think because it's something that is developing and coming about" (Participant 5, consultant pediatric rheumatologist). "I've been on nothing very specific to JIA and pain assessment… there's nothing out there" (Participant 6, nurse).
Pain assessment knowledge is acquired through observation of other departmental practices.	"It's more just shadowing of what techniques are being used" (Participant 16, occupational therapist).
The lack of pain training leads to low confidence in assessment.	"Some people haven't done any pain training…they feel uncomfortable asking" (Participant 5, consultant pediatric rheumatologist).
Rheumatologists do not consider themselves best placed for pain assessment and/or communication because they do not ask the right questions.	"We as doctors are not necessarily good at exploring pain, we don't ask the right questions. And the other thing is whether or not we as doctors sat in clinic prescribing medicines are the right people to be assessing pain. Have we been trained properly, no, we've not been trained at all" (Participant 9, consultant pediatric rheumatologist).
There is a perception that therapists are best placed for pain assessment because they have more time, are less formal and have more regular contact with patients. Therapists feel that patients with pain are sent to them because rheumatologists do not have the skills to address pain.	"I think allied health professionals ask the same sort of questions as the rheumatologists…perhaps we have more time and it might not feel as formal… we might be seeing them more regularly" (Participant 2, occupational therapist). "And I think that is a lot because they don't feel like they have the skills, so they send them to us" (Participant 13, physical therapist).
Theme 2: Reluctance to engage in pain discussions	
Subthemes	
Evaluation of children's pain is done without asking directly about it. Pain experiences are noticeable through discussions about other aspects of the condition.	"Very seldom do I ask a child about their pain" (Participant 11, physical therapist). "I get a feel for how much pain they've been in. Do I need more information about their pain? I'm not sure I do" (Participant 7, consultant pediatric rheumatologist).
Asking about pain may lead to amplification of pain through exaggerated responses or heightened perceptions.	"Indirectly, I get the information anyway, without saying, are you in pain, which feels like I'm leading them into saying, yes I am" (Participant 2, occupational therapist). "That's what they'll ask, are you in pain? And you know what children are like. Yeah, yeah. They're not really. They're running around, left, right and centre" (Participant 10, nurse).
HCP's fear making the pain worse by drawing attention to it (physically or emotionally).	"Eventually if you're asked enough times, well, yes, maybe I do have pain…. nagging them about pain isn't necessarily in their best interest… we educate them about pain and suddenly they all have it" (Participant 5, consultant pediatric rheumatologist).
Pain assessment and discussions can lead to poorer well-being.	"I don't ask in every consultation because that can be quite demoralising, demoting" (Participant 11, physical therapist).
Managing reported pain is difficult; there are a lack of resources and time.	"Some people don't ask about pain because they don't want to get stuck with having to deal with it" (Participant 5, consultant pediatric rheumatologist). "It's alright me asking about their pain, but then do I have the facility to deal with it?" (Participant 3, pediatrician). "I think the perception of pain is often one whereby people seek to avoid it. I hope it's not because of ignorance…they're just not wanting to open that can of worms. I think it's more related to work based pressures and time" (Participant 20, physical therapist).

* JIA = juvenile idiopathic arthritis; HCP = health care professional.

assessments of disease activity and that disease activity needs to be assessed first, even if that did not leave time for pain assessment. Functional assessments and markers of disease activity were judged to be the highest priority measurements for participants involved in managing JIA in children and young people. This again reflects participants' attention to pain in the context of levels of inflammatory disease activity and interference with function. In some cases, participants reported that they would make assumptions about the severity of pain based solely on measures of disease activity and functional assessments. There seemed to be little awareness in these accounts that pain levels may act independently of disease activity markers.

Theme 4: Beliefs about pain in JIA (Table 4). Most of the HCPs interviewed believed that persistent pain was not an intrinsic feature of JIA and that HCPs should generally avoid reinforcing the perception that it is such a feature. It was felt that active JIA was not necessarily painful, a view which may have led to patients' accounts of pain being discredited. Several participants indicated that when patients reported pain, their JIA would not be

Table 4. Themes 3 and 4, subthemes, and associated interview excerpts*

Themes and subthemes	Interview excerpts
Theme 3 : Low prioritization of pain assessment	
Subthemes	
Low prioritization of pain assessment in clinical consultations	"I don't think we should dwell on pain" (Participant 2, occupational therapist). "I wouldn't ask at every appointment, how has your pain been? I very much try to work away from that" (Participant 4, physical therapist). "So we tend to not to, I suppose, prioritise pain so much" (Participant 8, consultant pediatric rheumatologist). "It's an important factor, but it's not the first on the list" (Participant 6, nurse).
Other priority assessments include measures of function and disease activity	"It's stiffness, lack of function, and lack of movement you're looking for" (Participant 11, physical therapist). "In clinical practice you're very much assessing degree of inflammation evident, and again that's very much on physical examination plus or minus some blood tests" (Participant 15, consultant pediatric rheumatologist).
Theme 4: Beliefs about pain in JIA	
Subthemes	
Pain symptoms not a part of having JIA as active JIA is not painful; arthritis is not the underlying cause of pain in those who complain	"From a consultant rheumatologist point of view, they will feel quite strongly that active JIA should not be painful, and will often give that message, which kind of leads people to feel that people are not getting it, they're not believed" (Participant 4, physical therapist). "Whenever I teach other doctors about JIA I always say pain is not particularly a feature… I think a lot of patients with arthritis don't complain of much pain… often when patients complain of pain, arthritis isn't the problem" (Participant 8, consultant pediatric rheumatologist).
HCP perception that pain should be proportionate to disease activity	"When they come in, it's part of their disease process. When they're controlled, they don't have pain… it is disease activity. And then you hope that it doesn't go on to, like we've said, with chronic pain" (Participant 10, nurse). "What would make you think that a child has amplified their pain report?" (Interviewer). "Well, if their reports of pain seem out of proportion to what I find on clinical examination" (Participant 7, consultant pediatric rheumatologist).
Disregard of JIA diagnosis in light of persistent pain complaints	"And again, we just have to see chronic pains. And chronic pains are the children that have got pain… when you examine them, they've got no evidence of active arthritis" (Participant 10, nurse).
Focus on pain is unhelpful for those who have chronic pain	"With the JIAs, if I think that they may be tipping into a bit of a chronic pain and they are very focused on the pain, I'll maybe try and not talk about pain" (Participant 13, physical therapist).
Lack of evidential pain in those with seemingly inactive arthritis	"People have different opinions of chronic pain patients than of JIA. They see somebody with a real condition and JIA is an inflammatory condition, whereas chronic pain, there might not always be something to see" (Participant 17, physical therapist).

* See Table 3 for definitions.

the underlying cause. This assumption seemed to be based upon the perception that patients with arthritis do not complain about much pain. In some cases, this led to participants believing that patients with arthritis did not complain about pain while reporting that in their own practice, they rarely asked about or were reluctant to engage in discussions about pain.

Most of the accounts reflected the belief that pain symptoms caused by JIA are directly proportionate in severity to clinically observed levels of disease activity. There were also strong perceptions that if disease activity processes were controlled then the pain would consequently be reduced. Accounts and descriptions of pain that were given during the interviews tended to reflect a "medical model" of pain, that is, the view that pain stems directly from the site of disease or injury, and that pain severity is in proportion to the degree of injury. Most HCPs described managing quite a high number of children and young people with JIA whose reported pain was viewed as disproportionate in the context of the clinical examination. If children and young people reported levels of pain that were not congruent with their measures of disease activity (suggesting low levels of inflammation) then an additional or even an alternative diagnosis of chronic pain was suggested. Throughout interviews, HCPs referred to 2 distinct groups of patients in rheumatology. The first group are those with active JIA with directly proportionate pain. The second group are patients with well-controlled JIA but for whom pain remains a problem; it was here that JIA diagnosis seemed to be decoupled from the pain experiences. In those cases, the patient's focus on pain was viewed as the underlying problem. Furthermore, there was not always evidence of the underlying disease those viewed as having chronic pain, whereas for those with JIA, the pain was referred to as more "real."

Theme 5: Treatment of pain (Table 5). There was a strong belief that pharmacologic management of JIA would reduce the amount of pain that children and young people experienced. On further examination, we found that this was more evident in the accounts given by rheumatologists and less likely to appear in the therapists' accounts. In addition, therapists were more likely to express greater concerns about an "overly-medicalized" approach

Table 5. Themes 5 and 6, subthemes, and associated interview excerpts*

Themes and subthemes	Interview excerpts
Theme 5: Treatment of pain	
Subthemes	
Pharmacologic management of JIA will reduce pain levels	"If I treat the swelling, then the pain will get better, I don't really think of it as a distinct entity" (Participant 1, trainee rheumatologist). "Well I suppose in managing the disease with steroids or other management you are treating the pain" (Participant 19, physical therapist).
Over-medicalizing the treatment of pain in JIA	"It is all about the medication. It is all about the injections. I think the hospital system is so medical" (Participant 12, occupational therapist).
Referral of patients elsewhere (therapy or specialist pain services) when pain did not respond to medication	"They (rheumatologists) are very interested in the JIAs because they can give them medicine. Some of the mechanical pain and the hyper mobility and the chronic pains they just palm them…you know, they are just not interested" (Participant 13, physical therapist). "Some consultants will spend more time asking about the pain, some will acknowledge it's there but then pass onto physiotherapy… if it's an inflammatory thing then we want to medically manage that, and if it's not then we should pass them onto physio or psychology" (Participant 21, trainee rheumatologist). Interviewer: "When you say chronic pain patient, would you describe what you mean?" Participant 6 (Nurse): "So they're patients that…every single day they're in pain with no focus… generally it's everywhere…their attendance at school or work or life activities is very low." Interviewer: "Mm. What about if they were a JIA patient but that's under control and…?" Participant 6 (Nurse): "And…but there's still a chronic pain? I'd still do the same. Still do the same referral to the same people-to the pain service."
Theme 6: Undervaluing pain reports	
Subthemes	
Negative responses from HCPs towards patients with chronic pain	"With the chronic pains, I always think you can see people smiling or raising their eyebrows about it" (Participant 10, nurse). "There are times that people will roll their eyes at certain patients, because they're in pain" (Participant 18, nurse).
Undervaluing seriousness and unsympathetic responses to pain	"Arthritis pain is awful but never that awful, I don't think" (Participant 1, trainee pediatric rheumatologist).
Conscious efforts to think about the broader context of pain and consider reports seriously	"Even though in the back of your mind you are fairly certain it's gonna be just chronic pain that you're dealing with, you've also got to take it seriously" (Participant 20, physical therapist).
Difficulties trying to objectively evaluate CYP pain	"You immediately feel anxious as soon as pain comes up… it can be so hugely over-reported and so difficult to make sense of" (Participant 9, consultant pediatric rheumatologist). "And it's really difficult…you are basically making a judgement about whether their reaction to what happened is proportionate or not" (Participant 13, physical therapist).
Questioning the credibility of pain reports, e.g., is there a financial gain, disability benefit and/or more attention from significant others	"If there's a financial reward to them having pain…they get benefits for it if they're perceived as being disabled" (Participant 12, occupational therapist). "Some patients might play on it, they get more attention" (Participant 16, occupational therapist).

* CYP = children and young people. See Table 3 for other definitions.

to JIA management and treatment of symptoms. This was the only theme in which we found potential evidence of discipline or profession-specific beliefs expressed.

Study participants talked about the importance of referring JIA patients with persistent pain (which HCPs perceived as "noninflammatory") to services for patients outside rheumatology. Some of the therapists perceived these referrals from rheumatologists as indicating a lack of rheumatologists' interest in pain management. In contrast, some rheumatologists implied that while they acknowledged the presence of pain, they felt that they did not have the relevant skill set to manage noninflammatory pain. If a medical management approach of disease did not work to reduce pain, there was a view that pain could only be managed through these other, more specialized pain services.

Theme 6: Undervaluing pain (Table 5). Many HCPs had created their own terms to label children and young people with persistent pain that could not be treated through medical management of arthritis, such as referring to these patients as having "chronic pains." HCPs reported noticing negative responses from other HCPs when these patients were seen in clinic such as eye-rolling, smiling, or raising eyebrows, behaviors that seemed to signify that these patients' reports of pain were unconvincing. Some HCPs in the study appeared to minimize the seriousness or relevance of chronic pain and the importance of how severe suffering could be for children and young people with persistent pain.

There were suggestions that chronic pain might not always be taken seriously in clinical contexts and that it needed a conscious effort from the HCP to think about the broader

context of that pain. Pain symptoms seemed to be undervalued because of the difficulties associated with evaluating pain severity objectively in children and young people. Participants perceived their role to include making judgments about participant's reactions to pain and described this challenge as anxiety provoking.

HCPs believed that there were benefits for patients or families who overreported or exaggerated the severity of pain symptoms, and this further complicated HCPs' task of making sense of pain. These benefits could be financial reward, disability benefit, and/or more attention from significant others. These findings suggested that HCPs often questioned the credibility of patients' pain reports and the potential advantages for each patient who reported more pain than participants thought was appropriate.

DISCUSSION

This is, to our knowledge, the first study to explore HCPs' beliefs about the role of pain in JIA and the prioritization of pain assessment in patients with this long-term condition. Findings suggest that professionals managing JIA in children and young people are largely working from a somewhat outmoded model of pain as something that should be directly and proportionately related to degree of disease activity. Alternative, more complex, and current models of pain conceptualize subjective pain experiences as the result of bidirectional interactions involving biologic, psychological, and contextual processes (27). These approaches recognize that sensory pain inputs are filtered by a variety of mechanisms, both biologic and psychological, such as genetic predispositions, prior learning, emotional status, and context. Acknowledgment of these processes was missing in the accounts of pain in children and young people with JIA given by many professionals interviewed in our study.

Our findings indicate that for some HCPs, their "personal models" of pain associated with JIA may not be congruent with research findings, which suggest that pain acts independently of levels of disease activity in JIA (7,16,17). A personal model of illness can be defined as an individuals' beliefs, emotions, knowledge, experiences, and behaviors (28) and are important in shaping the conceptualizations of children and young people and their parents of the condition (29). In JIA, the importance of developing a comprehensive understanding of pain, including how and when to treat it and when to ignore or persist with activities despite pain, is essential for effective pain management.

It is apparent from our findings that understanding from pain theory and patients' experiences have not been translated into current practice. It is important that assessment and management of pain is incorporated into clinical practice alongside the assessment and management of the disease. Our research suggests that a paradigm shift is needed in approaches to pain assessment and communication by professionals managing JIA in children and young people. Pain assessment scores can affect later pain management decisions (30). Pain may, in some instances, be best managed in other services. However, if initial presentation occurs in pediatric rheumatology then it is important that the pain management needs of these patients have been assessed and communicated before appropriate referrals are made.

Overall, our study demonstrated that HCPs' beliefs about the role of pain in JIA may be a factor determining how or whether they feel able to support patients to manage pain symptoms. This study demonstrates that for these HCPs, pain assessment was not always a major part of clinical consultations with JIA patients. In a study by Guzman et al (12), comparison of the priorities of children and HCPs in JIA assessment found that pain was of medium importance to HCPs. However, our study finds pain and its assessment to be of low priority compared to other clinical assessments in this group of participants, and there appeared to be a reluctance for some HCPs to initiate conversations about pain. Similar to a study by Fitzcharles et al (31), our study found that HCPs concentrated on measurement of underlying disease mechanisms, as disease activity measures took precedent.

One potential limitation of the current study is that data were only drawn from participants working in the UK national health care system. It is interesting to consider our findings in the light of UK clinical practice guidelines. There are no performance standards for pain assessment in the UK (13) and no recommendation to assess pain as an indicator of disease improvement (32) or therapeutic response (33) in pediatric rheumatology. Even where a recommendation to routinely assess pain has been given as one of the standards of care for JIA (34), no guidance is given about how to assess pain.

Our research demonstrates that the recognition of pain assessment should be a higher priority in pediatric rheumatology in the UK. The findings of our study identify some of the attitudinal and practical barriers to achieving such a priority level.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Lee had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Lee, Rashid, Thomson, Cordingley.
Acquisition of data. Lee, Cordingley.
Analysis and interpretation of data. Lee, Rashid, Thomson, Cordingley.

REFERENCES

1. Petty R, Southwood T, Manners P, Baum J, Glass D, Goldenberg J, et al. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. J Rheumatol 2004;31:390–2.

2. Clinch J, Eccleston C. Chronic musculoskeletal pain in children: assessment and management. Rheumatology (Oxford) 2009;48: 466–74.
3. Schanberg L, Lefebvre J, Keefe F, Kredich D, Gil K. Pain coping and the pain experience in children with juvenile chronic arthritis. Pain 1997;73:181–9.
4. Lalloo C, Stinson J. Assessment and treatment of pain in children and adolescents. Best Pract Res Clin Rheumatol 2014;28:315–30.
5. Thastum M, Herlin T. Pain-specific beliefs and pain experience in children with juvenile idiopathic arthritis: a longitudinal study. J Rheumatol 2011;38:155–60.
6. Sherry DD, Bohnsack J, Salmonson K, Wallace CA, Mellins E. Painless juvenile rheumatoid arthritis. J Pediatr 1990;116:921–4.
7. Schanberg LE, Anthony KK, Gil KM, Maurin EC. Daily pain and symptoms in children with polyarticular arthritis. Arthritis Rheum 2003;48:1390–7.
8. Benestad B, Vinje O, Veierød MB, Vandvik IH. Quantitative and qualitative assessments of pain in children with juvenile chronic arthritis based on the Norwegian version of the pediatric pain questionnaire. Scand J Rheumatol 1996;25:293–9.
9. Secor-Turner M, Scal P, Garwick A, Horvath K, Wells CK. Living with juvenile arthritis: adolescents challenges and experiences. J Pediatr Health Care 2011;25:302–7.
10. Connelly M, von Baeyer CL. Pain as a quality of care measure in juvenile idiopathic arthritis: one step forward, but is it the best foot [letter]? Arthritis Care Res (Hoboken) 2011;63:1352–3.
11. Tong A, Jones J, Craig JC, Singh-Grewal D. Children's experiences of living with juvenile idiopathic arthritis: a thematic synthesis of qualitative studies. Arthritis Care Res (Hoboken) 2012;64:1392–404.
12. Guzman J, Gomez-Ramirez O, Jurencak R, Shiff N, Berard R, Duffy C, et al. What matters most for patients, parents and clinicians in the course of juvenile idiopathic arthritis? A qualitative study. J Rheumatol 2014;41:2260–9.
13. Simons JM, Macdonald LM. Pain assessment tools: children's nurses' views. J Child Health Care 2004;8:264–78.
14. Kimura Y, Walco GA, Sugarman E, Conte PM, Schanberg LE. Treatment of pain in juvenile idiopathic arthritis: a survey of pediatric rheumatologists. Arthritis Rheum 2006;55:81–5.
15. Rapoff MA, Lindsley CB. Pain. In: Cassidy JT, Petty RE, Laxer RM, Lindsley CB, editors. Textbook of pediatric rheumatology. 6th ed. Philadelphia: Saunders; 2011. p. 193–7.
16. Lomholt J, Thastum M, Herlin T. Pain experience in children with juvenile idiopathic arthritis treated with anti-TNF agents compared to non-biologic standard treatment. Pediatr Rheumatol Online J 2013;11:21.
17. Malleson PN, Oen K, Cabral DA, Petty RE, Rosenberg AM, Cheang M. Predictors of pain in children with established juvenile rheumatoid arthritis. Arthritis Care Res (Hoboken) 2004;51:222–7.
18. Ilowite N, Walco G, Pochaczevsky R. Assessment of pain in patients with juvenile rheumatoid arthritis: relation between pain intensity and degree of joint inflammation. Ann Rheum Dis 1992;51:343–6.
19. Chira P, Schanberg L. Inflammatory arthritis and arthropathy. In: McGrath P, Stevens B, Walker S, Zempsky W, editors. Oxford textbook of paediatric pain. 1st ed. Oxford: Oxford University Press; 2014. p. 215–28.
20. Garcia-Munitis P, Bandeira M, Pistorio A, Magni-Manzoni S, Ruperto N, Schivo A, et al. Level of agreement between children, parents, and physicians in rating pain intensity in juvenile idiopathic arthritis. Arthritis Rheum 2006;55:177–83.
21. Sprangers MA, Aaronson NK. The role of health care providers and significant others in evaluating the quality of life of patients with chronic disease: a review. J Clin Epidemiol 1992;45:743–60.
22. Stinson J, Jibb L, Nguyen C, Nathan P, Maloney A, Dupuis L, et al. Development and testing of a multidimensional iPhone pain assessment application for adolescents with cancer. J Med Internet Res 2013;15:1–15.
23. Baildam E, Davidson J. BSPAR position statement on professionals working paediatric rheumatology. Rheumatology (Oxford) 2008;47:743–4.
24. Ritchie J, Spencer L. Qualitative data analysis for applied policy research. In: Bryman A, Burgess R, editors. Analysing qualitative data. London: Routledge; 1994. p. 173–94.
25. Gale N, Heath G, Cameron E, Rashid S, Redwood S. Using the framework method for the analysis of qualitative data in multi-disciplinary health research. BMC Med Res Methodol 2013;13:1–8.
26. British Society for Rheumatology. The state of play in UK rheumatology: insights into service pressures and solutions. UK: British Society for Rheumatology; 2015. p. 1, 29–31.
27. Gatchel RJ, Bo Peng Y, Peters ML, Fuchs PN, Turk DC. The biopsychosocial approach to chronic pain: scientific advances and future directions. Psychol Bull 2007;133:581–624.
28. Skelton JA, Croyle RT. Mental representation in health and illness. New York: Springer-Verlag; 1991.
29. Phillips LA, Leventhal H, Leventhal EA. Physicians' communication of the common-sense self-regulation model results in greater reported adherence than physicians' use of interpersonal skills. Br J Health Psychol 2012;17:244–57.
30. Dalton JA, Blau W. Changing the practice of pain management: an examination of the theoretical basis of change. Pain Forum 1996;5:266–72.
31. Fitzcharles MA, Almahrezi A, Shir Y. Pain: understanding and challenges for the rheumatologist [review]. Arthritis Rheum 2005;52:3685–92.
32. Giannini EH, Ruperto N, Ravelli A, Lovell DJ, Felson DT, Martini A. Preliminary definition of improvement in juvenile arthritis. Arthritis Rheum 1997;40:1202–9.
33. Ruperto N, Martini A. International research networks in pediatric rheumatology: the PRINTO perspective. Curr Opin Rheumatol 2004;16:566–70.
34. Arthritis and Musculoskeletal Alliance. Standards of care for children and young people with juvenile idiopathic arthritis. April 2010. URL: http://arma.uk.net/wp-content/uploads/pdfs/Juvenile%20Idiopathic%20Arthritis.pdf.

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Juvenile Sjögren's Syndrome: Clinical Characteristics With Focus on Salivary Gland Ultrasonography

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Objective. Juvenile Sjögren's syndrome (SS) is a rare, poorly defined, and possibly underdiagnosed condition affecting children and adolescents. The aim of this study was to characterize symptoms and clinical findings of juvenile SS and to explore the clinical application of major salivary gland ultrasonography (SGUS) in patients with juvenile SS.

Methods. A cross-sectional multicenter study recruited patients with disease onset until age 18 years (n = 67). Disease characteristics were recorded, and unstimulated whole sialometry and SGUS examination of the parotid and submandibular salivary glands were performed.

Results. The female:male ratio was 58:9. The mean age at first symptom was 10.2 years and 12.1 years at diagnosis. Ocular and oral symptoms were noted in 42 of 67 patients (63%) and 53 of 66 patients (80%), respectively. The American-European Consensus Group or American College of Rheumatology/European League Against Rheumatism classification criteria for primary SS were fulfilled by 42 of 67 patients (63%). Pathologic SGUS findings were observed in 41 of 67 patients (61%); 26 of 41 SGUS+ patients (63%) fulfilled primary SS criteria. Salivary gland enlargements/parotitis were noted in 37 of 58 patients and were nonsignificantly associated with SGUS+ status (P = 0.066). The mean levels of saliva were 5.6 ml/15 minutes in SGUS– patients compared to 3.3 ml/15 minutes in the SGUS+ patients (P = 0.049). A total of 36 of 41 SGUS+ patients (88%) were anti-Ro/La+ compared to 14 of 26 SGUS– patients (54%) (P = 0.001). In addition, 24 of 39 SGUS+ patients (62%) were positive for rheumatoid factor (RF), whereas only 5 of 25 SGUS– patients (20%) were RF+ (P = 0.001).

Conclusion. Juvenile SS is characterized by a large spectrum of clinical symptoms and findings. Several glandular and extraglandular parameters such as hyposalivation, swollen salivary glands, and autoantibodies are associated with pathologic SGUS findings.

INTRODUCTION

Primary Sjögren's syndrome (SS) is a systemic autoimmune disorder. Patients with primary SS experience oral and ocular dryness and extraglandular manifestations such as fatigue, arthralgia, and arthritis (1). In addition to subjective and objective findings of salivary and/or lacrimal gland involvement, the primary SS classification is based on either the presence of autoantibodies against Ro/SSA and/or La/SSB, and/or focal mononuclear cell inflammation with a focus score ≥1 in a minor labial salivary gland biopsy (2). Serum autoantibodies have been presented as early markers of primary SS (3).

Juvenile SS is a rare, poorly defined and possibly underdiagnosed condition (4,5). The mean age at the time of diagnosis is approximately 10 years (6). A common initial symptom is swelling of the major salivary glands (6,7). Several organ systems may be affected, resulting in neurologic, dermatologic, musculoskeletal, vascular, gastrointestinal, respiratory, renal, and hema-

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SIGNIFICANCE & INNOVATIONS

- Interest in juvenile Sjögren's syndrome is increasing and international collaborations are emerging. To date, to the best of our knowledge, this is the largest cohort world-wide characterizing juvenile Sjögren's syndrome and also the first large study investigating salivary gland ultrasonography in this patient group.

tologic manifestations (8,9). Extraglandular manifestations occur in approximately 50% of children with juvenile SS (4). Criteria for juvenile SS are not available in current literature (10–12), and neither the American-European Consensus Group (AECG) criteria (2) nor the American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) criteria (13) have been validated in a juvenile population. In addition, the AECG criteria may not be applicable due to diverse clinical manifestations in children compared to adults (5).

Interest regarding the major salivary glands ultrasonography examination (SGUS) (14) as a diagnostic tool for primary SS is increasing (15–19). SGUS may serve as a supplement, or even alternative, to minor salivary gland biopsy (11,17). Development of a noninvasive, diagnostic method for evaluation of the salivary gland component, to aid the diagnosis of juvenile SS, is especially important in the younger population, both with regard to the late onset in some patients of sicca symptoms and the current lack of diagnostic criteria. Previous studies have indicated that SGUS may be of value in establishing a juvenile SS diagnosis (7,20,21). However, current reports include small numbers of patients, and SGUS application remains to be evaluated in a larger cohort. Further studies on juvenile SS are needed, and to our knowledge, our study is, to date, the largest cohort for this patient group. The aim of this study was to characterize symptoms and clinical findings in patients with juvenile SS and to investigate SGUS as a diagnostic tool for juvenile SS.

MATERIALS AND METHODS

Patients. The study design was a cross-sectional multicenter study. Patients were recruited from Haukeland University Hospital in Bergen, Norway, Oslo University Hospital in Oslo, Norway, Hospital General Universitario Gregorio Marañón in Madrid, Spain, Hospital Universitário Cassiano Antônio Moraes of Federal University of Espírito Santo in Vitória, Brazil, Hospital Universitário Clementino Fraga Filho of Federal University of Rio de Janeiro in Rio de Janeiro, Brazil, Hospital das Clinicas, Faculdade de Medicina da Universidade de Sao Paulo in Sao Paulo, Brazil, University Medical Center Groningen in Groningen, The Netherlands, and University of Florida, Gainesville, Florida. Patients had previously received the diagnosis of juvenile SS by a specialist in rheumatology or pediatric medicine at age ≤18 years. At the time of inclusion, all patients were younger than 25 years. Identification of patients at each clinic was performed by the local specialist in rheumatology or pediatric medicine.

A clinical examination, sialometry, and SGUS were performed in all patients. Upon inclusion, patients were asked for information on extraglandular manifestations, and a medical history was collected from medical charts, including information regarding autoantibodies, biopsy results, and current/previous treatment.

Patients recruited in Norway (n = 11), Spain (n = 5), and Brazil (n = 40) were examined and included by the primary investigators (SDH and MVJ) with the local specialist. Patients recruited from The Netherlands (n = 8) and US (n = 3) were examined in collaboration with local experts and included retrospectively. Because this was a cross-sectional study, not all clinical examinations and tests had been performed or were available in all patients.

Disease activity measurements. Subjective symptoms and the EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI) score (22) were determined upon inclusion. Children were aided by an accompanying parent/guardian, when necessary. The European League Against Rheumatism Sjögren's Syndrome Disease Activity Index (ESSDAI) score (23) was registered upon inclusion. The hematologic and biologic domains were determined from the most recent blood samples available.

Tear secretion. Tear secretion was evaluated by the Schirmer I test. Wetting of the strip was recorded in mm, with levels of ≤5 mm wetting of the paper strip considered as pathologically reduced tear secretion.

Sialometry. Salivary gland functional capacity was evaluated by unstimulated sialometry, measured in ml/15 minutes, with the patients fasting for 90 minutes prior to examination. The volume of saliva was determined by weighing, with 1 gram corresponding to 1 ml. Saliva secretion levels ≤1.5 ml/15 minutes were considered pathologically reduced.

Salivary gland ultrasonography. The SGUS examination of the parotid and submandibular glands was performed using linear high-frequency transducers (6–15 MHz) and a simplified scoring system. Glandular homogeneity and the presence of hypoechogenic areas were evaluated and graded (range 0–3). Grades 0–1 were considered to correspond to normal/nonspecific changes and grades 2–3 to correspond to pathologic changes (Figure 1). The SGUS was performed and scored bedside by local experts in the US and The Netherlands and by SDH and MVJ in Norway, Spain, and Brazil.

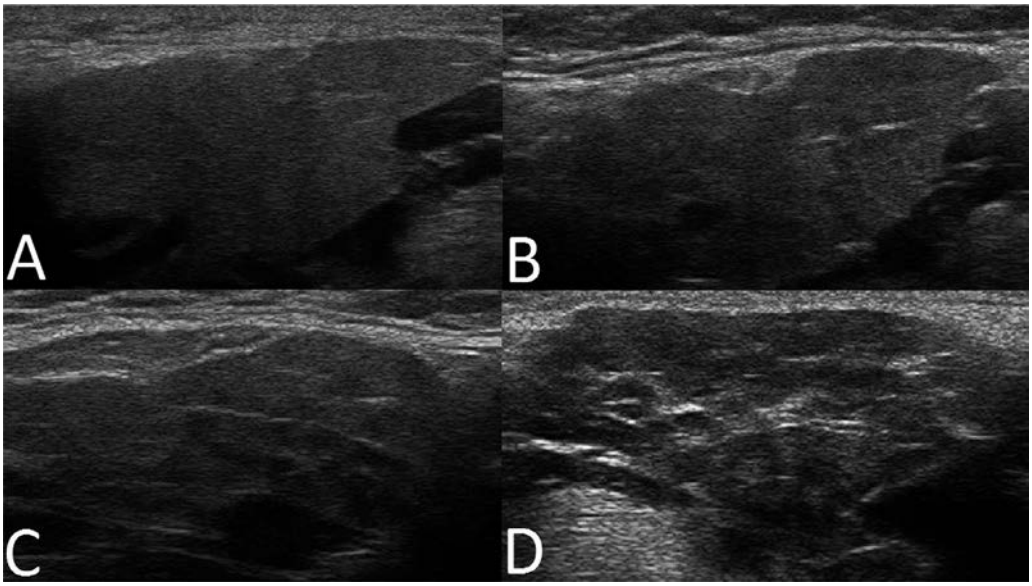

Figure 1. Representative major salivary gland ultrasonography images of submandibular glands, illustrating **A**, grade 0; **B**, grade 1; **C**, grade 2; and **D**, grade 3, with grades 0–1 corresponding to normal-appearing morphology, and grades 2–3 corresponding to pathologic changes in the submandibular and parotid glands of patients with clinical symptoms of juvenile Sjögren's syndrome.

Ethical considerations. This study was performed in accord with the regional medical and health research ethics regulations, and necessary applications were approved by the regional Committees in the participating centers/countries (Norway: 145/96-44.96, 242.06 2009/686; Brazil: 4478 701544787015447870151.433.660/201644787015.6.2001.0068). Informed consent was obtained from all participants and from parents of patients age <16 years, according to the Declaration of Helsinki. Parents/legal guardians of underaged patients were present at inclusion (clinical examination and SGUS imaging). In Spain, The Netherlands, and US, the non-invasive study design and number of patients included were in accordance with regional ethical guidelines and did not need a specific project approval.

Statistical analysis. Student's *t*-test with Welch's correction was used to study differences between groups and Pearson's correlation for the relationship between 2 variables. Correlations within ranges 0.0 to <0.2 were considered as poor, 0.2 to <0.4 as fair, 0.4 to <0.6 as moderate, 0.6 to <0.8 as good, and 0.8–1.0 as excellent. For categorical data, chi-square analysis was employed. To adjust for Type I error due to multiple comparisons, Benjamin-Hochberg adjustment was applied. All analyses were performed using SPSS statistics software, version 19.0.

Table 1. Patient demographics and associated diseases in all included patients (n = 67) with a clinical diagnosis of juvenile Sjögren's syndrome*

	No.	Mean ± SD years	SGUS–	SGUS+	*P*†	Benjamin-Hochberg adjustment
Age at inclusion, years	67	16.3 ± 4.7‡	17.3 ± 5.7	15.6 ± 3.9	0.146	NS
Age at first symptom, years	64§	10.2 ± 3.7	10.5 ± 4.5	10.1 ± 3.2	0.675	NS
Age at diagnosis, years	61§	12.1 ± 3.8	12.0 ± 4.5	12.2 ± 3.3	0.875	NS
Time from symptom onset to diagnosis, years	60§	1.8 ± 1.9	1.5 ± 1.5	1.9 ± 2.0	0.355	NS
Time from diagnosis to inclusion, years	61§	4.1 ± 4.4‡	5.5 ± 5.3	3.3 ± 3.5	0.062	NS
Female:male ratio	58:9	–	25:1	33:8	0.067	NS
Hypothyroidism, no./total (%)¶	5/59 (8)	–	3/25 (12)	2/34 (6)	0.404	NS
SLE, no./total (%)¶	7/59 (12)	–	4/25 (16)	3/34 (9)	0.400	NS
MCTD, no./total (%)¶	1/59 (2)	–	1/25 (4)	0/34 (0)	0.240	NS

* Values are the mean ± SD unless indicated otherwise. SGUS = salivary gland ultrasonography; NS = nonsignificant; SLE = systemic lupus erythematosus; MCTD = mixed connective tissue disease.
† *P* values are for the comparison of SGUS+ and SGUS– patients.
‡ Regional differences (patients included in Brazil compared to patients included in Europe/US).
§ Data not available from all patients.
¶ Number of positive observations/number of available observations.

RESULTS

Patient characteristics. Our cohort consisted of 67 patients. The female:male ratio was 58:9. Mean age at first symptom was 10.2 years (range 1–17), with 12.1 years at diagnosis (range 4–18), and 16.3 years at inclusion (range 6–25) (Table 1).

Of the 67 patients, 35 (52%) and 39 (58%) fulfilled the AECG (2) and ACR/EULAR (13) classification criteria, respectively. When combining the criteria, 32 patients (48%) fulfilled both sets of criteria and 42 patients (63%) fulfilled either the AECG or the ACR/EULAR criteria. One patient had mixed connective tissue disease (MCTD), and 7 patients were diagnosed with systemic lupus erythematosus (SLE) (Table 1).

In the patients with MCTD/SLE (n = 8), 7 presented with autoantibodies and fulfilled the AECG and the ACR/EULAR classification criteria. In this subgroup, 6 of 8 patients had ocular symptoms and 5 had ocular signs. All patients had experienced major salivary gland swelling, and 6 had salivary gland involvement by sialometry (n = 2), scintigraphy (n = 2), sialometry and scintigraphy (n = 1), or sialometry, scintigraphy, and sialography (n = 1). Five had available minor salivary gland biopsy results; the 3 patients lacking biopsy results had objective evidence of salivary gland involvement, either by a positive scintigraphy (n = 1), sialometry and scintigraphy (n = 1), or sialometry, scintigraphy, and sialography (n = 1). All 5 biopsy results were positive, i.e., with a focus score of ≥1, corresponding to ≥1 chronic inflammatory cell foci consisting of 50 or more cells per 4 mm^2 of otherwise normal-appearing minor salivary gland tissue. In comparison, for the remaining patients not diagnosed with an additional connective tissue disease (n = 59), information on minor salivary gland biopsy

Table 2. Subjective ocular and oral symptoms, objective signs of impaired tear secretion, salivary gland inflammation and hypofunction, serum autoantibodies, and fulfillment of classification criteria in all included patients (n = 67) with juvenile Sjögren's syndrome*

	No.	SGUS–	SGUS+	*P*†	Benjamin-Hochberg adjustment
Ocular symptoms (I)	42/67 (63)‡	23/26 (88)	19/41 (46)	0.001	Significant
Oral symptoms (II)	53/66 (80)	18/26 (69)	30/40 (75)	0.607	NS
Salivary gland enlargement	37/58 (64)§	12/24 (50)	25/34 (74)	0.066	NS
Ocular signs (III)	33/65 (51)‡	16/24 (67)	17/41 (41)	0.05	NS
Schirmer I test (ever)	27/64 (42)¶	13/25 (52)	14/39 (36)	0.203	NS
Ocular staining score	20/37 (54)	12/18 (67)	8/19 (42)	0.134	NS
Focus score ≥1 (IV)	28/34 (82)	7/8 (88)	21/26 (81)	0.662	NS
Focus score, mean ± SD	1.7 ± 1.7 (n = 20)	1.0 ± 0	1.9 ± 1.9	0.368	NS
Salivary gland involvement (V)	41/61 (67)#	21/26 (81)	20/35 (57)	0.052	NS
UWS ≤1.5 ml/minute	20/60 (33)¶	9/26 (35)	11/34 (32)	0.854	NS
UWS, mean ± SD ml/15 minutes	4.3 ± 4.6 (n = 60)	5.6 ± 5.8	3.3 ± 3.2	0.049	NS
Sialography	1/3 (33)**	1/2 (50)	0/1 (0)	0.386	NS
Sialo-scintigraphy	29/31 (9)††	20/22 (91)	9/9 (100)	0.350	NS
SGUS	41/67 (61)‡‡	–	–	–	–
Autoantibodies (VI)	50/67 (75)‡	14/26 (54)	36/41 (88)	0.002	Significant
ANA	62/67 (93)§	23/26 (88)	39/41 (9)	0.312	NS
Anti-Ro/SSA	50/67 (75)§§	14/26 (54)	36/41 (88)	0.002	Significant
Anti-La/SSB	27/67 (40)‡‡	4/26 (15)	23/41 (56)	0.001	Significant
Anti-Ro/SSA and anti-La/SSB	27/67 (40)‡‡	4/26 (15)	23/41 (56)	0.001	Significant
Anti-Ro/SSA or anti-La/SSB	50/67 (75)§§	14/26 (54)	36/41 (88)	0.002	Significant
Rheumatoid factor	29/64 (45)‡	5/25 (20)	24/39 (62)	0.001	Significant
AECG criteria	35/67 (52)	14/26 (54)	21/41 (51)	0.834	NS
ACR/EULAR criteria	39/67 (58)	15/26 (58)	24/41 (59)	0.946	NS
ACR/EULAR and AECG criteria	32/67 (48)	13/26 (50)	19/41 (46)	0.770	NS
ACR/EULAR or AECG criteria	42/67 (63)	16/26 (62)	26/41 (63)	0.877	NS

* Values are the number of patients with positive findings/patients with available information (%), unless indicated otherwise. Roman numerals indicate the corresponding items of the American-European Consensus Group (AECG) criteria. Regional differences refer to patients included in Brazil compared to patients included in Europe/US. SGUS = salivary gland ultrasonography; NS = nonsignificant; UWS = unstimulated whole saliva flow; ANA = antinuclear antibody; ACR = American College of Rheumatology; EULAR = European League Against Rheumatism.
† *P* values are for the comparison of SGUS+ and SGUS– patients.
‡ Regional differences.
§ Eight patients with systemic lupus erythematosus (SLE)/mixed connective tissue disease (MCTD).
¶ Four patients with SLE/MCTD.
# Six patients with SLE/MCTD, and 5 patients with SLE/MCTD, with regional differences.
** One patient with SLE/MCTD, with regional differences.
†† Four patients with SLE/MCTD, with regional differences.
‡‡ Three patients with SLE/MCTD, with regional differences.
§§ Seven patients with SLE/MCTD, with regional differences.

results was available from 29 patients, with a positive biopsy result in 23 cases. Among these, the accurate focus score was available from 16 patients, and 15 biopsy results were positive (focus score ≥1). All MCTD/SLE patients had extraglandular manifestations and 3 had renal affection, findings that were not registered in any of the other patients.

Subjective symptoms. Subjective ocular and oral dryness symptoms were noted in 42 of 67 patients (63%) and 53 of 66 patients (80%), respectively (Table 2). Only 8 of 66 patients (12%) reported no dryness symptoms. Ocular signs were noted in 26 of 40 patients (65%) with ocular symptoms ($P = 0.004$).

Subjective oral symptoms were not associated with a positive minor salivary gland biopsy result or objective salivary gland involvement (sialometry, sialography, or scintigraphy). Sialo-scintigraphy and/or sialography had been performed in 31 patients (Table 2), although only in the Brazilian part of the cohort.

The ESSPRI score for dryness correlated nonsignificantly with age at inclusion ($P = 0.062$; n = 58). The mean ESSPRI score for patients not fulfilling classification criteria (n = 25) was 2.7 compared to 4.0 for patients (n = 40) fulfilling either AECG and/or ACR/EULAR classification criteria for primary SS ($P = 0.04$).

Major salivary gland imaging and glandular characteristics. Pathologic SGUS findings (Figure 1 C and D) were observed in 41 of 67 patients. The mode SGUS score was 2 for all glands. The total sum of the SGUS score for all 4 glands (range 0–12) correlated with the ACR/EULAR points (r = 0.321, $P = 0.016$; n = 56) (Figure 2). SGUS+ findings were observed in 26 of 27 of the European and North American patients as compared to 15 of 40 of the Brazilian patients ($P = 0.001$).

Subjective sicca symptoms were not associated with pathologic SGUS findings; ocular symptoms were noted only in 19 of 41 SGUS+ patients (46%) compared to 23 of 26 SGUS– patients (88%) ($P = 0.001$). Ocular signs were noted in 17 of 41 SGUS+ patients (41%) compared to 16 of 24 SGUS– patients (67%) ($P = 0.050$). Oral symptoms were noted in 30 of 40 SGUS+ patients (75%) compared to 18 of 26 SGUS– patients (69%) ($P = 0.607$).

Salivary gland involvement (sialometry, sialo-scintigraphy, and sialography) was noted in 41 of 61 patients (67%), 20 of 35 SGUS+ patients (57%), and 21 of 26 SGUS– patients (81%) ($P = 0.052$) (Table 2). When considering the individual items for salivary gland involvement, unstimulated whole saliva levels (ml/15 minutes) correlated inversely with the sum of the SGUS score (range 0–12) for all 4 glands (r = –0.324, $P = 0.015$ [n = 56]) (Figure 2), and with the SGUS score (range 0–3) for both submandibular glands (r = –0.372, $P = 0.005$ [n = 56], and r = –0.301, $P = 0.024$ [n = 56], right and left gland, respectively). A correlation was also observed in the right parotid gland (r = –0.285, $P = 0.033$ [n = 56]). The mean level of saliva was 5.6 ml/15 minutes

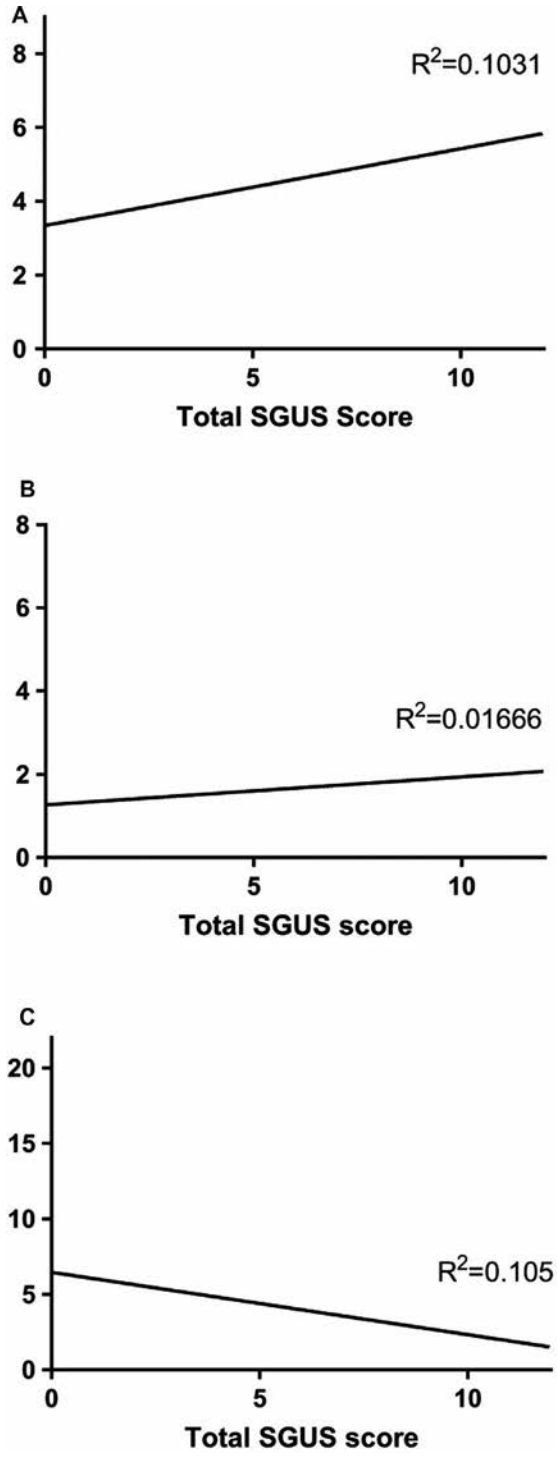

Figure 2. Total major salivary gland ultrasonography score (range 0–12) for all 4 glands in relation to the **A**, Total points of the American College of Rheumatology/European League Against Rheumatism classification criteria (range 0–9) ($P = 0.016$), **B**, Focus score, and **C**, Unstimulated whole saliva flow (range 0–21.36 ml/15 minute) ($P = 0.015$). The correlations were not significant after Benjamin-Hochberg adjustment. We did not find a correlation with the focus score (range 0–8).

in SGUS– patients compared to 3.3 ml/15 minutes in the SGUS+ patients ($P = 0.049$), but when comparing saliva cutoff levels (≤1.5 ml/15 minutes) SGUS+ patients were below the threshold in 11 of 34 cases (32%), compared to 9 of 26 SGUS– patients (35%) ($P = 0.854$). Scintigraphy findings coincided with both normal and pathologic SGUS findings ($P = 0.350$) (Table 2).

Information regarding minor labial salivary gland biopsy results was available in 34 patients. Among these, 28 of 34 patients (82%) had a focus score ≥1, 21 of 26 SGUS+ patients (81%) compared to 7 of 8 SGUS– patients (88%) ($P = 0.662$) (Table 2). For 20 patients, the precise focus score was available, ranging from 0 to 8 with a mean of 1.7. The mean focus score was 1.9 in the SGUS+ patients (n = 16) compared to 1.0 in the SGUS– patients (n = 4), but the difference was not statistically significant ($P = 0.368$), most likely due to low numbers. Low numbers probably also influenced the lack of correlation between precise focus score and total SGUS score, both when considering the glands separately and for all glands (Figure 2).

In total, 37 of 58 patients (64%) had experienced salivary gland enlargements/parotitis (Table 2), and although not significant, a trend was noted with regard to pathologic SGUS findings; 25 of 34 SGUS+ patients (74%) had experienced salivary gland swelling, compared to 12 of 24 SGUS– patients (50%) ($P = 0.066$).

Autoantibodies. The majority of patients, 50 of 67 (75%), presented with anti-Ro/SSA and/or anti-La/SSB. In the group with SGUS+ findings, 36 of 41 patients (88%) were anti-Ro/SSA positive, whereas in the SGUS– group only 14 of 26 patients (54%) were anti-Ro/SSA positive ($P = 0.002$). Similarly, SGUS+ status was associated with anti-La/SSB; 23 of 41 of the SGUS+ patients (56%) were anti-La/SSB+, whereas only 4 of 26 of the SGUS– patients (15%) were anti-La/SSB+ ($P = 0.001$), and 24 of 39 of the SGUS+ patients (62%) were positive for rheumatoid factor (RF), whereas only 5 of 25 of the SGUS– patients (20%) were RF+ ($P = 0.001$) (Table 2).

In total, 11 of 36 SGUS+ patients (31%) with positive anti-Ro/SSA status did not fulfill the current classification criteria for primary SS (2,13). Of these 11 patients, all did not fulfill or were lacking 1 or several items; ocular symptoms (n = 11, 3 positive), oral symptoms (n = 10, 7 positive), ocular signs (n = 11, all negative), minor salivary gland biopsy

Table 3. Extraglandular manifestations in patients with juvenile Sjögren's syndrome*

	No.	SGUS–	SGUS+	*P*†	Benjamin-Hochberg adjustment
Extraglandular manifestations	56/62 (90)‡	24/25 (96)	32/37 (86)	0.214	NS
Constitutional	24/59 (41)§	12/25 (48)	12/34 (35)	0.326	NS
Cutaneous	17/59 (29)¶	8/25 (32)	9/34 (26)	0.643	NS
Lymphadenopathy	35/59 (59)#	17/25 (68)	18/34 (53)	0.245	NS
Articular	34/59 (58)**	17/25 (68)	17/34 (50)	0.167	NS
Muscular	5/59 (8)	1/25 (4)	4/34 (12)	0.290	NS
Pulmonary	1/59 (2)	1/25 (4)	0/34 (0)	0.240	NS
Renal	3/59 (5)††	1/25 (4)	2/34 (6)	0.745	NS
Peripheral nervous system	1/59 (2)	1/25 (4)	0/34 (0)	0.240	NS
Central nervous system	3/59 (5)	3/25 (12)	0/34 (0)	0.038	NS
Hematologic domain	16/58 (28)¶	6/24 (25)	10/34 (29)	0.711	NS
Biologic domain	21/58 (36)‡‡	9/24 (38)	12/34 (35)	0.863	NS
ESSPRI score, mean ± SD	3.5 ± 2.5 (n = 65)	3.2 ± 2.8	3.7 ± 2.3	0.368	NS
ESSPRI dryness, mean ± SD	3.4 ± 3.0 (n = 65)	3.4 ± 2.9	3.5 ± 3.1	0.919	NS
ESSPRI fatigue, mean ± SD	4.3 ± 3.4 (n = 65)§§	3.8 ± 3.9	4.6 ± 3.0	0.314	NS
ESSPRI pain, mean ± SD	2.9 ± 3.2 (n = 65)	2.4 ± 3.4	3.2 ± 3.2	0.362	NS
Total ESSDAI score, mean ± SD	4.7 ± 5.4 (n = 62)	3.4 ± 2.8	5.5 ± 6.5	0.138	NS
Clinical ESSDAI, mean ± SD	3.2 ± 4.1 (n = 59)	2.7 ± 3.0	3.6 ± 4.8	0.443	NS

* Values are the number of patients with positive findings/patients with available information (%), unless indicated otherwise. Regional differences refer to patients included in Brazil compared to patients included in Europe/US. SGUS = salivary gland ultrasonography; NS = nonsignificant; ESSPRI = European League Against Rheumatism (EULAR) Sjögren's Syndrome Patients Reported Index; ESSDAI = EULAR Primary Sjögren's Syndrome Disease Activity Index.
† *P* values are for the comparison of SGUS+ and SGUS– patients.
‡ Eight patients with systemic lupus erythematosus (SLE)/mixed connective tissue disease (MCTD), with regional differences.
§ Five patients with SLE/MCTD, with regional differences.
¶ Five patients with SLE/MCTD.
# Three patients with SLE/MCTD, with regional differences.
** Eight patients with SLE/MCTD.
†† Three patients with SLE/MCTD.
‡‡ Six patients with SLE/MCTD.
§§ Regional differences.

(n = 3, all negative), salivary gland involvement (n = 6, 2 positive), sialo-scintigraphy (n = 1, positive), sialometry (n = 6, all negative), ocular staining score (n = 6, 1 positive). Six patients had experienced salivary gland swelling; 2 of these had also experienced lacrimal gland swelling.

Taking a closer look at patients not fulfilling classification criteria for primary SS (n = 25), 11 of 25 patients (44%) presented with anti-Ro/SSA and SGUS+ status, whereas the remaining patients (n = 14) were either SGUS+ but lacked anti-Ro/SSA (n = 4) or were anti-Ro/SSA– and had a normal-appearing SGUS (n = 10). Among the SGUS+/anti-Ro/SSA– patients, 2 of 4 were positive for antinuclear antibody (ANA). For the SGUS–/anti-Ro/SSA– patients, all had pathologic findings by sialo-scintigraphy, 9 of 10 (90%) were ANA+, 3 of 10 (30%) had pathologic levels of unstimulated whole saliva flow, and 1 also had a positive sialography. One of the SGUS–/anti-Ro/SSA– patients was diagnosed with SLE.

Extraglandular manifestations. Various extraglandular manifestations at some time point had been noted in 56 of 62 patients (90%) (Table 3). The mean ESSPRI score total was 4.0 for patients (n = 40) fulfilling classification criteria for primary SS (2,13) compared to 2.7 for the remaining patients (n = 25) (P = 0.040). The ESSPRI pain score was also increased in patients fulfilling the AECG and/or ACR/EULAR classification criteria for primary SS, with mean levels of 3.5 compared to 1.9 (P = 0.05). The mean ESSDAI score was nonsignificantly higher in the SGUS+ patients compared to the SGUS– patients (P = 0.138) (Table 3).

Treatment. Symptomatic treatment was observed in 29 of 59 patients (49%) (Table 4). Symptomatic treatment was registered in 16 of 34 SGUS+ patients (47%) compared to 17 of 25 SGUS– patients (68%) (P = 0.109). Only 5 of 59 patients (8%) had received salivary substitutes; 4 of these patients had SGUS+ status. Three patients had received pilocarpine, none had received cevimeline. A higher number of patients, 30 of 59 (51%), had received or were using lacrimal substitutes, whereof the majority, 18 of 30 (60%), had normal SGUS (P = 0.005) (Table 4). The mean ESSPRI score for dryness was 4.1 for patients who had received symptomatic treatment compared to 2.4 for those without symptomatic treatment (P = 0.028).

Current or previous use of nonsteroidal antiinflammatory drugs was noted in 16 of 34 SGUS+ patients (47%) compared to 9 of 25 SGUS– patients (36%) (P = 0.396). Of 59 patients, 54 were currently

Table 4. Treatment in all included patients with juvenile Sjögren's syndrome*

	No.	SGUS–	SGUS+	P†	Benjamin-Hochberg adjustment
Symptomatic treatment, current	29/59 (49)‡	17/25 (68)	16/34 (47)	0.109	NS
Symptomatic treatment, ever	47/59 (80)§	22/25 (88)	25/34 (74)	0.172	NS
Salivary substitutes, current	4/59 (7)	1/25 (4)	3/34 (9)	0.466	NS
Salivary substitutes, ever	5/59 (8)	1/25 (4)	4/34 (12)	0.466	NS
Lacrimal substitutes, current	25/59 (42)¶	16/25 (64)	9/34 (26)	0.004	Significant
Lacrimal substitutes, ever	30/59 (51)¶	18/25 (72)	12/34 (35)	0.005	Significant
NSAIDS, current	9/59 (15)	1/25 (4)	8/34 (24)	0.039	NS
NSAIDs, ever	25/59 (42)#	9/25 (36)	16/34 (47)	0.396	NS
Systemic treatment, ever	56/59 (95)**	25/25 (100)	31/34 (91)	0.127	NS
Systemic treatment, current	46/59 (78)††	23/25 (92)	23/34 (68)	0.026	NS
Hydroxychloroquine, ever	54/59 (92)**	25/25 (100)	29/34 (85)	0.045	NS
Hydroxychloroquine, current	40/59 (68)**	22/25 (88)	18/34 (53)	0.004	Significant
MTX, ever	22/57 (39)#	9/25 (36)	13/32 (41)	0.722	NS
MTX, current	14/57 (25)#	6/25 (24)	8/32 (25)	0.931	NS
Azathioprine, ever	12/58 (21)‡‡	6/25 (24)	6/33 (18)	0.588	NS
Azathioprine, current	10/58 (17)§§	5/25 (20)	5/33 (15)	0.628	NS
Low prednisone, ever	31/57 (54)§	11/24 (46)	20/33 (61)	0.269	NS
Low prednisone, current	12/57 (21)¶¶	4/24 (17)	8/33 (24)	0.489	NS
High prednisone, ever	13/59 (22)‡	6/25 (24)	7/34 (21)	0.755	NS
High prednisone, current	5/59 (8)§§	2/25 (8)	3/34 (9)	0.911	NS

* Values are the number of patients with positive findings/patients with available information (%), unless indicated otherwise. Regional differences refer to patients included in Brazil compared to patients included in Europe/US. SGUS = salivary gland ultrasonography; NS = nonsignificant; NSAIDs = nonsteroidal antiinflammatory drugs; MTX = methotrexate.
† P values are for the comparison of SGUS+ and SGUS– patients.
‡ Six patients with systemic lupus erythematosus (SLE)/mixed connective tissue disease (MCTD), with regional differences.
§ Six patients with SLE/MCTD.
¶ Five patients with SLE/MCTD, with regional differences.
# One patient with SLE/MCTD.
** Eight patients with SLE/MCTD.
†† Eight patients with SLE/MCTD, with regional differences.
‡‡ Four patients with SLE/MCTD, with regional differences.
§§ Four patients with SLE/MCTD.
¶¶ Five patients with SLE/MCTD.

(n = 40) or previously (n = 14) treated with hydroxychloroquine. In total, 29 of 34 SGUS+ patients (85%) had experience using hydroxychloroquine, whereas 25 of 25 SGUS– patients had used or were using hydroxychloroquine (P = 0.045). When instead comparing never users (n = 5) and previous users (n = 14) to current users (n = 40), 18 of 34 SGUS+ patients (53%) and 22 of 25 SGUS– patients (88%) were on current treatment (P = 0.004) (Table 4).

Systemic treatment was noted in 56 of 59 patients (95%) and was associated with extraglandular manifestations in 52 of 53 patients (P = 0.001). In 10 patients, systemic treatment was ceased, and 42 of 53 patients with extraglandular manifestations were currently receiving systemic treatment (P = 0.481). In 40 of 46 patients (87%), the systemic treatment was current hydroxychloroquine (P = 0.001).

DISCUSSION

To date, this is the largest study investigating clinical characteristics of patients with juvenile SS in combination with SGUS. The female:male ratio was approximately 6.4:1, i.e., slightly altered with more male patients as compared to 9:1 for adults with primary SS (24–27). The mean time from symptom debut to diagnosis was 1.8 years, naturally shorter than in adult primary SS patients, where the time from debut of symptoms to diagnosis spans up to 11–14 years (26).

Nearly 2 of 3 of the patients fulfilled the current classifications criteria for primary SS, and there were no significant differences in the application of the 2002 AECG (2) and the ACR/EULAR criteria (13). Due to different practices between regions and the fact that not all examinations in the classification criteria are routinely performed in all pediatric patients, we cannot be certain that patients not fulfilling the classification criteria in this study would still not fulfill criteria were all necessary examinations performed.

SGUS findings were associated with anti-Ro/SSA and anti-La/SSB, similar to previous findings in adult primary SS (28). Of the 36 SGUS+ patients with positive anti-Ro/SSA, 11 patients did not fulfill the AECG or ACR/EULAR classification criteria due to lack of objective salivary or lacrimal gland involvement, such as reduced salivary and/or lacrimal secretion. Of these 11 patients, 6 of 8 had registered salivary gland enlargement.

When considering the patients not fulfilling classification criteria for primary SS (n = 25), 11 (44%) were anti-Ro/SSA+ and SGUS+, 4 (16%) were SGUS+ and anti-Ro/SSA–, and 10 (40%) were anti-Ro/SSA– and SGUS–. Among the anti-Ro/SSA– patients, 11 of 14 (78.6%) were ANA+. In addition, all the anti-Ro/SSA– and SGUS– patients had previously documented salivary gland involvement by sialo-scintigraphy. Our findings thus support the notion that the existing criteria for primary SS are not optimal for clinical evaluation and research of juvenile SS (10,12,29). Of note, among the individuals fulfilling either the AECG or the ACR/EULAR classification criteria, 1 of 42 SGUS+ patients was ANA+ but anti- Ro/SSA–. Concerning the individuals fulfilling both AECG and ACR/EULAR criteria, all 19 SGUS+ patients were anti-Ro/SSA+ compared to 11 of 13 of the SGUS– patients (P = 0.077). Other relevant autoantibodies such as anti-La/SSB and RF were also associated with SGUS findings, further supporting the link between autoantibodies and salivary gland involvement in juvenile SS.

In this cohort of patients with juvenile SS, pathologic SGUS changes (61%) were slightly more common compared to findings in adults (30) and nonsignificantly associated with salivary gland swelling, a clinical feature generally associated with juvenile SS. Similar to findings in adult primary SS, a higher SGUS score was associated with lower levels of unstimulated whole saliva (28), nonsignificantly associated with oral dryness symptoms. Treatment of oral dryness symptoms was rare, but linked to SGUS+ status in 4 of 5 cases. Ocular sicca symptoms and symptomatic treatment of dry eye were more common in SGUS– patients. The ESSPRI dryness score showed a trend to increase with age at inclusion (P = 0.062). One might speculate whether this increase was due to actual later onset of sicca symptoms, or whether oral dryness is not perceived as a problem by the younger patients.

Although the mean focus score was higher in SGUS+ patients compared to SGUS– patients and implies that the focus score can mirror the degree of damage visualized by SGUS, comparison of findings in the major and the minor glands was limited due to lack of data on minor salivary gland focus score.

Similar to earlier reports in both primary SS and juvenile SS, the patients in this cohort displayed a high degree of extraglandular manifestations (25,30). Both mean ESSPRI and mean ESSPRI pain scores were higher in the patients fulfilling AECG and ACR/EULAR classification criteria, and the mean ESSDAI score was nonsignificantly higher in the SGUS+ patients compared to the SGUS– patients.

Eight patients with extraglandular manifestations differed from their juvenile SS peers in several aspects. All 8 had at some point been diagnosed with SLE or MCTD and 3 had renal affection, an extraglandular manifestation with a varied prevalence of 2% to 67% in primary SS (31–33). Kidney involvement was not observed in any other patients in the cohort. Although 7 of 8 patients fulfilled the classification criteria for primary SS, a possible misdiagnosis cannot be ruled out, as differentiation between various connective tissue diseases can be difficult. Nonetheless, 3 of 8 patients with SLE/MCTD presented with SS-like SGUS changes, such as hypoechogenic areas and inhomogeneity (27), consistent with the frequency of imaging findings in this subgroup of the cohort.

Previous or current systemic treatment was also quite frequent, especially in patients with extraglandular manifestations. For the majority of patients, the current systemic treatment was hydroxychloroquine. Only 18 of 40 patients with current hydroxychloroquine treatment displayed SGUS+ changes, whereas 16 of 19 patients without current treatment showed changes. These results should, however, be interpreted with care because among those 2 groups there is both a higher proportion of patients with

extraglandular manifestations (39 of 40 versus 14 of 19, respectively) ($P = 0.005$), current systemic treatment (37 of 40 versus 9 of 19, respectively) ($P = 0.001$), and a lower degree of SGUS+ status in a subgroup of the cohort consisting of patients included in Brazil compared to Europe/US (15 of 40 versus 26 of 27) ($P = 0.000$), and a possible confounding factor cannot be ruled out. Patients in this Brazilian subgroup were also older when included, and the mean time from diagnosis to inclusion was higher.

Studying the current group of patients revealed variation in subjective symptoms, clinical findings, application of diagnostic tests/methods, and treatment regimes. More invasive diagnostic methods (such as sialo-scintigraphy and sialography, compared to sialometry) and systemic treatment (azathioprine and high dose corticosteroids/prednisone) were observed in the subgroup of the cohort consisting of patients included in Brazil, possibly due to a higher incidence of extraglandular manifestations.

The data presented in this study were a combination of newly acquired and retrospective data. In consequence, shortcomings include lack of new blood tests and incomplete clinical data, limiting the application of AECG and ACR/EULAR classification criteria. Different ultrasonography machines and probes were used for the SGUS examinations, possibly affecting the results obtained. To move forward, a prospective study with a more rigorous design, a more standardized regime for data collection, and international collaborations are necessary to characterize this rare condition and establish adequate criteria for diagnosis and classification.

In conclusion, findings in the juvenile SS patients studied indicate an association between SGUS results, hyposalivation, and autoantibodies. In many patients, SGUS status was also associated with salivary gland swelling, a previously known and common clinical finding in juvenile SS. SGUS is an interesting diagnostic tool for identifying patients with juvenile SS.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Hammenfors had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Analysis and interpretation of data. Hammenfors, Jonsson.

REFERENCES

1. Jonsson R, Bolstad AI, Brokstad KA, Brun JG. Sjögren's syndrome: a plethora of clinical and immunological phenotypes with a complex genetic background. Ann N Y Acad Sci 2007;1108:433–47.
2. Vitali C, Bombardieri S, Jonsson R, Moutsopoulos HM, Alexander EL, Carsons SE, et al. Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. Ann Rheum Dis 2002;61:554–8.
3. Johnsen SJ, Brun JG, Gøransson LG, Småstuen MC, Johannesen TB, Haldorsen K, et al. Risk of non-Hodgkin's lymphoma in primary Sjögren's syndrome: a population-based study. Arthritis Care Res (Hoboken) 2013;65:816–21.
4. Anaya JM, Ogawa N, Talal N. Sjögren's syndrome in childhood. J Rheumatol 1995;22:1152–8.
5. Lieberman SM. Childhood Sjögren syndrome: insights from adults and animal models. Curr Opin Rheumatol 2013;25:651–7.
6. Cimaz R, Casadei A, Rose C, Bartunkova J, Sediva A, Falcini F, et al. Primary Sjögren syndrome in the paediatric age: a multicentre survey. Eur J Pediatr 2003;162:661–5.
7. Fang QG, Liu FY, Sun CF. Recurrent submandibular gland swelling as a first manifestation in a child with primary Sjögren syndrome. J Craniofac Surg 2013;24:e413–5.
8. Nikitakis NG, Rivera H, Lariccia C, Papadimitriou JC, Sauk JJ. Primary Sjögren syndrome in childhood: report of a case and review of the literature. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2003;96:42–7.
9. Bogdanovic R, Basta-Jovanovic G, Putnik J, Stajic N, Paripovic A. Renal involvement in primary Sjögren syndrome of childhood: case report and literature review. Mod Rheumatol 2013;23:182–9.
10. Schuetz C, Prieur AM, Quartier P. Sicca syndrome and salivary gland infiltration in children with autoimmune disorders: when can we diagnose Sjögren syndrome? Clin Exp Rheumatol 2010;28:434–9.
11. Yokogawa N, Lieberman SM, Alawi F, Bout-Tabaku S, Guttenberg M, Sherry DD, et al. Comparison of labial minor salivary gland biopsies from childhood Sjögren syndrome and age-matched controls. J Rheumatol 2014;41:1178–82.
12. Houghton K, Malleson P, Cabral D, Petty R, Tucker L. Primary Sjögren's syndrome in children and adolescents: are proposed diagnostic criteria applicable? J Rheumatol 2005;32:2225–32.
13. Shiboski CH, Shiboski SC, Seror R, Criswell LA, Labetoulle M, Lietman TM, et al. 2016 American College of Rheumatology/European League Against Rheumatism classification criteria for primary Sjögren's syndrome: a consensus and data-driven methodology involving three international patient cohorts. Arthritis Rheum 2017;69:35–45.
14. De Vita S, Lorenzon G, Rossi G, Sabella M, Fossaluzza V. Salivary gland echography in primary and secondary Sjögren's syndrome. Clin Exp Rheumatol 1992;10:351–6.
15. Obinata K, Sato T, Ohmori K, Shindo M, Nakamura M. A comparison of diagnostic tools for Sjögren syndrome, with emphasis on sialography, histopathology, and ultrasonography. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2010;109:129–34.
16. Milic VD, Petrovic RR, Boricic IV, Marinkovic-Eric J, Radunovic GL, Jeremic PD, et al. Diagnostic value of salivary gland ultrasonographic scoring system in primary Sjögren's syndrome: a comparison with scintigraphy and biopsy. J Rheumatol 2009;36:1495–500.
17. Salaffi F, Argalia G, Carotti M, Giannini FB, Palombi C. Salivary gland ultrasonography in the evaluation of primary Sjögren's syndrome: comparison with minor salivary gland biopsy. J Rheumatol 2000;27:1229–36.
18. Cornec D, Jousse-Joulin S, Marhadour T, Pers JO, Boisrame-Gastrin S, Renaudineau Y, et al. Salivary gland ultrasonography improves the diagnostic performance of the 2012 American College of Rheumatology classification criteria for Sjögren's syndrome. Rheumatology (Oxford) 2014;53:1604–7.

19. Carotti M, Ciapetti A, Jousse-Joulin S, Salaffi F. Ultrasonography of the salivary glands: the role of grey-scale and colour/power Doppler. Clin Exp Rheumatol 2014;32 Suppl 80:S61–70.
20. Nieto-Gonzalez JC, Monteagudo I, Bello N, Martinez-Estupinan L, Naredo E, Carreno L. Salivary gland ultrasound in children: a useful tool in the diagnosis of juvenile Sjögren's syndrome. Clin Exp Rheumatol 2014;32:578–80.
21. Civilibal M, Canpolat N, Yurt A, Kurugoglu S, Erdamar S, Bagci O, et al. A child with primary Sjögren syndrome and a review of the literature. Clin Pediatr (Phila) 2007;46:738–42.
22. Lee J, Koh JH, Kwok SK, Park SH. The EULAR Sjögren's Syndrome Patient-Reported Index is an independent determinant of health-related utility values of Korean patients with primary Sjögren's syndrome. Clin Exp Rheumatol 2016;34:663–7.
23. Seror R, Bowman SJ, Brito-Zeron P, Theander E, Bootsma H, Tzioufas A, et al. EULAR Sjögren's syndrome disease activity index (ESSDAI): a user guide. RMD Open 2015;1:e000022.
24. Haugen AJ, Peen E, Hulten B, Johannessen AC, Brun JG, Halse AK, et al. Estimation of the prevalence of primary Sjögren's syndrome in two age-different community-based populations using two sets of classification criteria: the Hordaland Health Study. Scand J Rheumatol 2008;37:30–4.
25. Virdee S, Greenan-Barrett J, Ciurtin C. A systematic review of primary Sjögren's syndrome in male and paediatric populations. Clin Rheumatol 2017;36:2225–36.
26. Ramirez Sepulveda JI, Kvarnstrom M, Eriksson P, Mandl T, Norheim KB, Johnsen SJ, et al. Long-term follow-up in primary Sjögren's syndrome reveals differences in clinical presentation between female and male patients. Biol Sex Differ 2017;8:25.
27. Goransson LG, Haldorsen K, Brun JG, Harboe E, Jonsson MV, Skarstein K, et al. The point prevalence of clinically relevant primary Sjögren's syndrome in two Norwegian counties. Scand J Rheumatol 2011;40:221–4.
28. Hammenfors DS, Brun JG, Jonsson R, Jonsson MV. Diagnostic utility of major salivary gland ultrasonography in primary Sjögren's syndrome. Clin Exp Rheumatol 2015;33:56–62.
29. Yokogawa N, Lieberman SM, Sherry DD, Vivino FB. Features of childhood Sjögren's syndrome in comparison to adult Sjögren's syndrome: considerations in establishing child-specific diagnostic criteria. Clin Exp Rheumatol 2016;34:343–51.
30. Both T, Dalm VA, van Hagen PM, van Daele PL. Reviewing primary Sjögren's syndrome: beyond the dryness. From pathophysiology to diagnosis and treatment. Int J Med Sci 2017;14:191–200.
31. Bossini N, Savoldi S, Franceschini F, Mombelloni S, Baronio M, Cavazzana I, et al. Clinical and morphological features of kidney involvement in primary Sjögren's syndrome. Nephrol Dial Transplant 2001;16:2328–36.
32. Pertovaara M, Korpela M, Pasternack A. Factors predictive of renal involvement in patients with primary Sjögren's syndrome. Clin Nephrol 2001;56:10–8.
33. Vitali C, Bombardieri S, Moutsopoulos HM, Balestrieri G, Bencivelli W, Bernstein RM, et al. Preliminary criteria for the classification of Sjögren's syndrome: results of a prospective concerted action supported by the European Community. Arthritis Rheum 1993;36:340–7.

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Predicting Incident Radiographic Knee Osteoarthritis in Middle-Aged Women Within Four Years: The Importance of Knee-Level Prognostic Factors

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Objective. To develop and internally validate risk models and a clinical risk score tool to predict incident radiographic knee osteoarthritis (RKOA) in middle-aged women.

Methods. We analyzed 649 women in the Chingford 1,000 Women study. The outcome was incident RKOA, defined as Kellgren/Lawrence grade 0–1 at baseline and ≥2 at year 5. We estimated predictors' effects on the outcome using logistic regression models. Two models were generated. The clinical model considered patient characteristics, medication, biomarkers, and knee symptoms. The radiographic model considered the same factors, plus radiographic factors (e.g., angle between the acetabular roof and the ilium's vertical cortex [hip α-angle]). The models were internally validated. Model performance was assessed using calibration and discrimination (area under the receiver characteristic curve [AUC]).

Results. The clinical model contained age, quadriceps circumference, and a cartilage degradation marker (C-terminal telopeptide of type II collagen) as predictors (AUC = 0.692). The radiographic model contained older age, greater quadriceps circumference, knee pain, knee baseline Kellgren/Lawrence grade 1 (versus 0), greater hip α-angle, greater spinal bone mineral density, and contralateral RKOA at baseline as predictors (AUC = 0.797). Calibration tests showed good agreement between the observed and predicted incident RKOA. A clinical risk score tool was developed from the clinical model.

Conclusion. Two models predicting incident RKOA within 4 years were developed, including radiographic variables that improved model performance. First-time predictor hip α-angle and contralateral RKOA suggest OA origins beyond the knee. The clinical tool has the potential to help physicians identify patients at risk of RKOA in routine practice, but the tool should be externally validated.

INTRODUCTION

Knee osteoarthritis (OA) is one of the greatest contributors to global disability and a major global public health burden (1). It was the indication for surgery in 96% of the 98,147 primary knee-joint replacements conducted in the UK in 2016 (2). The current treatment for knee OA pain is limited to symptom relief with analgesics and/or physiotherapy. Preventing knee OA is thus an increased focus of public health.

Previous studies have identified risk factors for the incidence and progression of radiographic knee osteoarthritis (RKOA), such as older age, female sex, and higher body mass index (BMI) (3–6). However, only 3 prognostic models have been developed for incident RKOA (7–9). Two of these models were developed using 9

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SIGNIFICANCE & INNOVATIONS

- Identifying women with knees at high risk of developing radiographic knee osteoarthritis (RKOA) will enable preventive measures to be tested. To do so, we have developed clinical and radiologic predictive models for short-term incidence of RKOA.
- We have generated a risk score tool to help clinicians use the clinical model and inform their patients about their risk of developing RKOA.
- Both models and the risk score tool could be useful in identifying participants at risk of developing RKOA in the short-term for clinical trials.
- The radiographic model selected hip α-angle, bone mineral density at the spine lumbar, and contralateral knee OA as predictors of RKOA, suggesting OA origins beyond the knee area.

and 12 years of participant follow-up data (7,9). The most recent study followed participants for 5 years to identify rapid progression and considered radiographic tibiofemoral OA as the outcome (8).

Because the rate at which knee OA progresses varies considerably between patients (10), a model for short-term incident RKOA is needed to identify homogeneous phenotypes of patients, to facilitate forecasting and target potential treatments (11). Many of the known risk factors for RKOA have only been studied in isolation (12,13). Their combined effects and any other risk factors for the onset of short-term RKOA are needed to better identify those at risk.

To the best of our knowledge, this is the first study to asses a wide range of potential predictors that includes physical assessment, sociodemographic characteristics, medication, biomarkers, medical history (family history, knee pain, activity associated with a painful knee, and occupation), spine and hip radiographs and densitometries, and lifestyle. Incorporating new predictors in clinical prediction models adds value, improving the information available to clinicians and patients when deciding on preventive strategies to reduce rapid disease incidence. A description of patients at risk of rapid progression to RKOA will also help in selecting participants for randomized controlled trials of new interventions.

We aimed to develop and internally validate a prognostic model for short-term incidence of RKOA in a population-based cohort of women, focusing on knee-level risk factors. We also aimed to develop a clinical risk prediction tool to help clinicians identify women who are most likely to develop RKOA within 4 years.

MATERIALS AND METHODS

Data source and sample size. This study was carried out retrospectively using data from the Chingford 1,000 Women study. This is a well-described prospective population-based cohort of 1,003 women seen annually for osteoporosis and OA over 23 years (3). Women were selected from the age/sex register of a large general practice in Chingford, North London, UK. They lived in a middle-class area and were mostly white (98%) and middle-aged (ages 44–67 years). Women included in this analysis were recruited at the baseline between 1988 and 1989 and were seen again 4 years later.

Participants. The unit of analysis was the knee. Each woman participated with 1 or both knees, which were radiographed at baseline (year 1) and follow-up (year 5). Exclusion criteria for participants were any indication of inflammatory arthritis (rheumatoid arthritis or lupus) or a neurologic medical condition (poliomyelitis, Parkinson's disease, stroke, multiple sclerosis, or cerebral palsy) at baseline or year 10, because this information was not available for year 5. Fifty participants were excluded using these criteria. Individual knees were also excluded if they had a Kellgren/Lawrence (K/L) grade of 2 or more (14), an osteophyte (lateral or medial), or joint space narrowing (JSN) of grade ≥1 at baseline (10). The ethics committee approved the Chingford study (reference number: LREC R & WF 96), and written informed consent was obtained from each participant.

Outcome. The outcome was incident RKOA, defined as a knee with a K/L grade of 0 or 1 at baseline and of grade ≥2 at year 5. The K/L classification progresses from grade 0 to 4, based on radiographs (where 0 = normal, 1 = no JSN and possible osteophyte, 2 = possible JSN and definite osteophyte, 3 = definite JSN and multiple osteophytes, sclerosis, and possible bony deformity, and 4 = marked JSN, large osteophytes, severe sclerosis, and definite bony deformity) (15,16). The Chingford study collected weight-bearing anteroposterior-view radiographs of the knee for all participants at baseline and follow-up. These radiographs were used to assign each knee a K/L grade, using previously described protocols (3,17).

Predictor variables. The Chingford investigators collected approximately 700 variables at baseline. A panel of experts in OA research selected candidate predictors for RKOA from these variables in a 3-round Delphi process. Categorical variables with <5 values in at least 1 category and variables with a poor association with the outcome ($P > 0.2$) were excluded. The remaining potential predictors were used to develop the model. Supplementary Tables 1–6, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23932/abstract, list the potential predictors, and Supplementary Appendix 1, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.23932/abstract, describes how the predictors were assessed.

Statistical analysis. We developed the prediction model as follows (18,19). Step 1: to address the issue of missing data, we generated 50 imputed data sets (20). The linearity of continuous variables with incident RKOA was assessed using fractional polynomials. Step 2: we evaluated the independent associations between the potential predictor variables and RKOA incidence with

logistic regression, using clustered SEs at the person-level. Two hundred bootstrap samples with replacement were combined with the 50 imputed data sets. Within each bootstrap sample, automatic backward selection was applied, using a significance level of 0.157 (21), corresponding to the Akaike information criterion. Step 3: variables that appeared in at least 70% of the bootstrap samples were retained in the final models (22). We developed 2 models. The first only considered variables that clinicians routinely have access to: patient characteristics, medications, biomarker risk factors, and knee symptoms (clinical model). The second also considered radiographic variables (radiographic model).

Internal validation. We used 200 bootstrap samples with replacement, combined with multiple imputations, to assess bias-corrected estimates of predictive ability. Further details of the multiple imputation, bootstrapping, and internal validation methods are described in Supplementary Appendix 1, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23932/abstract.

Model performance. We assessed the models' predictive performance using calibration and discrimination measures (21). The area under the receiver characteristic curve (AUC) was used to assess discrimination. Calibration, how closely predicted risk corresponds with observed risk, was assessed visually using calibration plots.

Clinical scoring tool. We created a points-based risk-scoring tool from the clinical model for easy clinical use, using previously described methods (23,24). The tool estimates the short-term risk of incident RKOA. All analyses were conducted using Stata software, version 13.1. We followed the TRIPOD (Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis Or Diagnosis) guidelines to ensure correct reporting (25).

RESULTS

Study characteristics. We analyzed 1,184 knees from 649 women for whom radiographic data were available at baseline (year 1) and year 5. The participants' mean ± SD age was 54 ± 6 years. Figure 1 shows the selection criteria for the included knees and that 109 knees (9.2%; n = 95) had developed RKOA by year 5.

We excluded 20 categorical variables for having <5 observations in ≥1 category. Following univariable analysis, we excluded 53 of the possible variables (for univariable analysis results, see Supplementary Tables 1–6, available on the *Arthritis Care &*

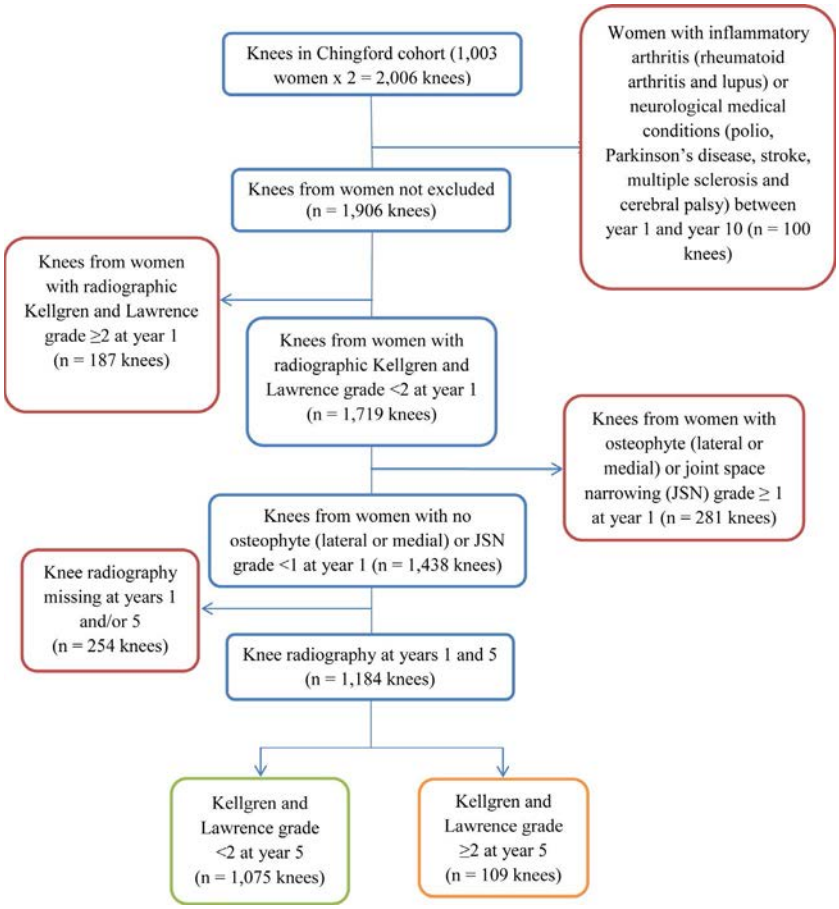

Figure 1. Flowchart showing selection criteria and number of excluded knees in which knee osteoarthritis developed within 4 years. JSN = joint space narrowing. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/acr.23932/abstract.

Table 1. Baseline features of knees that do and do not develop radiographic knee osteoarthritis (RKOA) in 4 years*

Patient features	No RKOA (n = 1,075)	RKOA (n = 109)	*P*
Age, median (IQR) years	53 (48, 58)	56 (51, 60)	<0.001†
Age at menopause, years			0.024
No menopause	278 (25.9)	21 (19.3)	–
<49	401 (37.3)	32 (29.4)	–
49–51	258 (24.0)	34 (31.2)	–
>51	138 (12.8)	22 (20.2)	–
BMI, median (IQR) kg/m^2	24.2 (22.5, 27.0)	26.4 (23.7, 28.9)	<0.001
Waist:hip ratio, median (IQR)	0.76 (0.73, 0.80)	0.78 (0.75, 0.81)	0.005
Weight at age 20 years, median (IQR) kg	54 (50, 60)	57 (53, 63)	0.002
Quadriceps circumference, median (IQR) cm‡	42 (39, 45)	44 (41, 47)	<0.001
Medication			
Oral contraceptive	363 (33.8)	29 (26.6)	0.130
Pain killers	79 (7.4)	13 (11.9)	0.089
Biomarkers			
CTX-II tertiles (corrected for creatinine), ng/ml	–	–	<0.001
52.7–133.1	294 (34.5)	14 (18.9)	–
133.2–229.8	290 (34.0)	19 (25.7)	–
≥229.9	268 (31.5)	41 (55.4)	–
Estradiol (E2), median (IQR) pmoles/liter	21 (20, 239)	20 (20, 153)	0.134§
Knee symptoms and height loss, stoop, or hump			
Duration, median (IQR) months‡	0 (0, 1)	0 (0, 12)	0.051¶
Presence of stiffness‡	247 (23.0)	34 (31.2)	0.055
Presence of pain‡	238 (22.1)	37 (33.9)	0.005
Presence of swelling‡	93 (8.6)	14 (12.8)	0.146
Injured knees for a week	81 (8.7)	19 (19.2)	0.001
Pain while walking	177 (19.1)	27 (27.3)	0.051
Pain while descending stairs	188 (20.2)	30 (30.3)	0.020
Pain while bending	188 (20.4)	28 (28.9)	0.051
Pain while sitting	112 (12.1)	19 (19.2)	0.043
Unstable knees	165 (17.8)	32 (33.0)	<0.001
Morning stiffness	233 (25.1)	33 (33.3)	0.077
Weather affects knees	157 (16.9)	28 (28.0)	0.006
Job/daily activities involved knee bending 10 years ago#	–	–	0.020
None/little/moderate	699 (71.8)	58 (60.4)	–
A lot/always	275 (28.2)	38 (39.6)	–
Loss of height, stoop, or hump	119 (11.1)	17 (15.6)	0.160
Radiology factors			
Baseline knee K/L grade‡	–	–	<0.001
0	1,029 (95.7)	75 (68.8)	–
1	46 (4.3)	34 (31.2)	–
Contralateral knee with RKOA at baseline‡	83 (7.7)	31 (28.4)	<0.001
Hip α-angle, mean ± SD degrees‡	55.4 ± 18.3	61.8 ± 22.7	0.004**
Spine osteophytes, no.	–	–	0.080
0–3	676 (66.3)	57 (57.6)	–
>3	343 (33.7)	42 (42.4)	–
Spine discs narrowing space, no.	–	–	0.027
0	900 (87.6)	79 (79.8)	–
>3	127 (12.4)	20 (20.2)	–
BMD Z-score at the spine L1–L4, mean ± SD	0.32 ± 1.25	0.86 ± 1.41	0.002

* Values are the number (%) unless indicated otherwise. RKOA was considered Kellgren/Lawrence (K/L) grade ≥2. These factors were considered potential prognostic factors in both the clinical and radiographic models. The data were collected in London, 1989 to 1991. IQR = interquartile range; BMI = body mass index; CTX-II = crosslinked C-telopeptide of type II collagen; BMD = bone mineral density.
† Significant F statistic.
‡ Side level.
§ Analysis of variance. Variances between groups were not equal.
¶ Significant F statistics (0.53) were excluded when there were no symptoms on the knee (values = 0).
# Collected at year 3.
** Analysis of variance. Bartlett's test for equal variances (*P* = 0.006).

Research web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23932/abstract). Missing data for the variables included in this study are shown in Supplementary Table 7, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.23932/abstract.

The remaining 30 potential predictors were used to develop the model, of which 24 are routinely available to clinicians and 6 are radiographic variables. Table 1 compares the 30 candidate risk factors between knees that developed RKOA within 4 years (by year 5) and those that did not. Supplementary Table 8, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23932/abstract, describes the 30 potential risk factors in greater detail.

Almost half of the 30 potential factors have been described previously (9,11,18–20). Sixteen were evaluated for the first time in the development of a model of RKOA incidence: age at menopause, waist-to-circumference ratio, weight at age 20 years, knee-level quadriceps circumference, painkiller use, duration of knee symptoms in months, stiffness during joint examination, pain during joint examination, swelling during joint examination, knees injured enough to rest them for a week, unstable knees (knees that give way), weather affecting knees, loss of height or a stoop or hump, number of thoracic and lumbar vertebrae with osteophytes or discs with narrowing space (26), and hip α-angle (the angle between the acetabular roof and the ilium's vertical cortex) (27).

Multivariable models predicting RKOA. The 24 of the 30 candidate predictors that are routinely available to clinicians (excluding the radiographic variables) were used to build the clinical multivariable model. Three candidates were identified as predictors ($P < 0.157$): older age, greater quadriceps circumference, and higher urine concentration of C-terminal telopeptide of type II collagen (CTX-II) corrected for creatinine at baseline (Table 2). The model is described by predicted probability of incident RKOA at year 5 = 1/(1 + exp [– (–10.54 + 0.06 × age + 0.11 × quadriceps circumference + 0.63 × CTX-II [≥229.9 ng/ml category])]).

All 30 candidate predictors, including the radiographic variables, were used to build the radiographic multivariable model. Seven candidate variables were identified as predictors ($P < 0.157$): older age, greater quadriceps circumference, presence of knee pain, K/L grade 1, contralateral RKOA at baseline, greater hip α-angle (28), and greater bone mineral density (BMD) Z-score at the spine (Table 2). The model is described by predicted probability of incident RKOA at year 5 = 1/(1 + exp [–11.64 + 0.07 × age + 0.09 × quadriceps circumference + 0.53 × knee pain (same side) + 1.88 × knee K/L grade 1 + 1.09 × contralateral knee with K/L grade ≥2 + 0.02 × hip α-angle + 0.28 × BMD Z-score at the spine L1–L4]).

Model performance. The upper panels of Figure 2 show the models' discrimination. The radiographic model (right upper panel) showed better discrimination (AUC = 0.809, optimism = 0.012, bias-corrected AUC = 0.797) than the more limited clinical model (left upper panel, AUC = 0.699, optimism = 0.007, bias-corrected AUC = 0.692).

Table 2. Multivariable logistic regression models identifying the predictors of radiographic knee osteoarthritis (RKOA) in women after 4 years of follow-up*

Intercept and predictors	Clinical model	Radiographic model
Intercept	2.64×10^{-5}	8.79×10^{-6}
Age, years	91; 1.06 (1.02–1.10)	78; 1.07 (1.02–1.12)
Quadriceps circumference, cm†	94; 1.11 (1.06–1.17)	91; 1.09 (1.03–1.15)
CTX-II tertiles, ng/ml (ref. 52.7–133.1) ≥229.9‡	85; 1.89 (1.13–3.14)	–
Presence of pain (ref. no)† Yes	–	73; 1.70 (0.99–2.90)
Baseline knee K/L grade (ref. grade 0)† Grade 1	–	100; 6.54 (3.62–11.83)
Contralateral knee with RKOA at baseline (ref. no)† Yes	–	95; 2.97 (1.65–5.33)
Hip α-angle, degrees†	–	95; 1.02 (1.01–1.03)
Z score BMD at the spine L1–L4	–	93; 1.32 (1.06–1.64)
AUC	0.699	0.809
Optimism	0.007	0.012
Bias-corrected AUC	0.692	0.797

* Values are the % retained; odds ratio (95% confidence interval), unless indicated otherwise. RKOA was considered Kellgren/Lawrence (K/L) grade ≥2. Retained indicates how often, as a percentage, a variable was retained in the final model after 200 bootstrapping attempts. CTX-II = crosslinked C-telopeptide of type II collagen; BMD = bone mineral density; AUC = area under the receiver characteristic curve.
† Side level.
‡ 133.2–229.8 ng/ml of urine CTX-II was retained only 3% of the time and was not considered for prediction.

The agreement between the predicted and observed values of incident RKOA at year 5 is shown in the lower panels of Figure 2 and was assessed visually. Both models showed good calibration: all of the 95% confidence interval bars and some of the mean values (data points) intersect with the 45° line that indicates perfect agreement between the predicted and observed RKOA at year 5. However, both models slightly overestimated some of the lowest values. Our models therefore estimated that fewer patients would develop RKOA than was observed in our sample for those patients who had a low probability of developing RKOA.

Clinical scoring tool. The clinical model with routinely available variables (age, quadriceps circumference, and urine CTX-II) was developed into a clinical scoring tool (Table 3). The tool gives scores from 0 (lowest risk) to 17 (greatest risk). A woman will reach the highest score if she is age 52–66 years, has a quadriceps with a circumference of 44–63 cm, and has a concentration of urine CTX-II of 0.23–1.34 μg/ml. We also

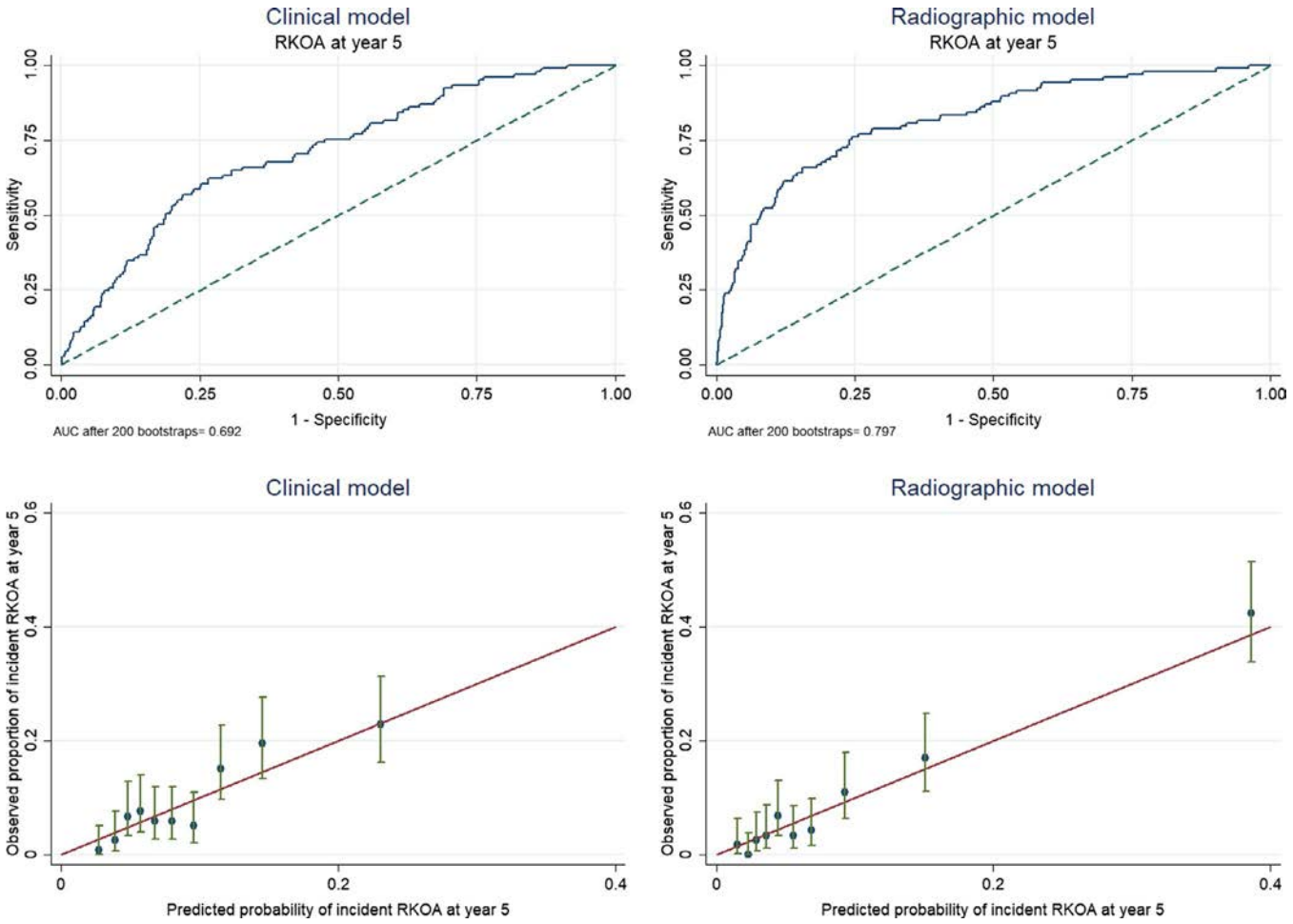

Figure 2. Discrimination and calibration plots with bias-corrected area under the receiver characteristic curve (AUC). Upper panels show discrimination when using age, quadriceps circumference, and urine crosslinked C-telopeptide of type II collagen (CTX-II) as predictors of incident radiographic knee osteoarthritis (RKOA; Kellgren/Lawrence grade ≥2) (clinical model; **left**), and when using age, quadriceps, painful knee, and radiologic factors as predictors (radiographic model; **right**). The area under the solid line and above the dotted line (line of no-discrimination) indicates the ability of the model to predict whether patients will develop RKOA within 4 years. Lower panels show the calibration of the imputed development data set for the clinical (**left**) and radiographic model (**right**). The sample used for validation was divided into 10 equal parts, according to their predicted risk. For each decile, the mean predicted risk is shown on the x-axis and the mean observed cases on the y-axis. The bars indicate 95% Agresti–Coull confidence intervals. The red straight line indicates perfect agreement between the observed and predicted values.

generated a tool that adds the 4 radiographic variables to the 3 routinely available variables, for those physicians with access to radiographs (see Supplementary Table 9, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23932/abstract).

DISCUSSION

We developed and internally validated 2 prediction models for incident RKOA in middle-aged women, one using information readily available to clinicians (clinical model) and the other supplementing this information with radiographic features (radiographic model). Both models showed good predictive validity, with bias-corrected AUCs of 0.692 (clinical model) and 0.797 (radiographic model). Calibration tests showed good agreement between the observed and predicted incident RKOA.

We also developed a clinical risk score tool to identify women at short-term risk of RKOA, using the predictors identified in the clinical model so that it can easily be used in clinical practice. A participant with a score of 5 would have a 30% ([5/17] × 100 = 29.4) probability of developing RKOA within 4 years. Higher risk is driven by the urine CTX-II marker. Patients with no risk from age (44–48 years) or quadriceps circumference (32–39 cm) but with high urine CTX-II (0.2–1.3 μg/ml) would have a 77% ([13/17] × 100 = 76.5) probability of developing RKOA within 4 years.

Older age, bigger quadriceps circumference, and elevated urine CTX-II were predictors of incident RKOA in the clinical model. When radiographic features, hip α-angle, and bone density were added to form the radiographic model, the predictive ability improved

Table 3. Risk score points system for identifying women at risk of developing radiographic knee osteoarthritis (RKOA) in the next 4 years, created using predictor variables identified in the clinical model*

Baseline risk factor	Regression coefficient	Reference value	Risk score	Final risk score†
Age, years	1.06	–	–	–
44–48	–	46	4	0
49–51	–	50	5	1
52–66	–	59	6	2
Quadriceps circumference, cm‡	1.11	–	–	–
32–39	–	35.5	3	0
40–43	–	41.5	4	1
44–63	–	53.5	5	2
CTX-II tertiles, μg/ml§	1.9	–	–	–
0.0527–0.1331	–	0.09	1	0
0.1332–0.2298	–	0.18	3	2
0.2299–1.3381	–	0.78	14	13

* RKOA was considered Kellgren/Lawrence grade ≥2. To calculate a patient's risk: 1) Find their measurement for each characteristic, 2) Circle the appropriate final risk score for each characteristic, 3) Add up the scores to give a total risk score, and 4) Convert the risk score to a % probability by dividing the score by the maximum possible (17) and multiplying by 100. CTX-II = crosslinked C-telopeptide of type II collagen.
† Score of 0 indicates lowest risk and score of 17 indicates greatest risk.
‡ Side level.
§ Original values in nanograms/ml transformed to micrograms/ml, i.e. divided by 1,000.

considerably, increasing from 69% to 80%. The radiographic model selected age and quadriceps circumference, similar to the clinical model, but did not select urine CTX-II. The radiographic model also selected knee pain, baseline K/L grade, contralateral knee with RKOA at baseline, hip α-angle, and Z score BMD at the spine L1–L4. The principal predictors (those with the highest odds ratios and strongest predictive ability) in the radiographic model were RKOA in the contralateral knee (3 times more associated with incidence RKOA than a contralateral knee free of RKOA) and K/L grade 1 in the index knee (6.5 times more related to incidence RKOA than the index knee with K/L grade 0), at baseline (Table 2).

Within the National Institute for Health and Care Excellence recommendations (29), patients with no pain or symptoms of knee OA who are age ≥45 years and have an activity associated with knee pain could be assessed using our clinical predictive tool to predict their risk of developing RKOA in the next 4 years. The radiographic predictive tool that includes radiographic variables could be useful in clinical practice if further investigation is undertaken when diagnosis is in doubt or in preparation for referral to a rheumatologist. Age (selected in both models) and knee pain (selected in the radiographic model) are both well-known risk factors for the incidence of RKOA (4,10,30–32).

Our models showed that a greater quadriceps circumference was associated with incidence RKOA. A larger circumference may reflect more subcutaneous fat around the knee. Individuals who are overweight may have added issues with load and muscle imbalance, which can lead to quadriceps inflammation (33,34). Measuring the quadriceps circumference in clinical practice is easy, making this a useful predictor (35).

As urine CTX-II is a by-product of the degradation of knee components such as matrix and cartilage, its presence has been associated with OA and osteoporosis (36). A meta-analysis that included the Chingford cohort used here showed that a higher likelihood of incident knee OA was associated with higher levels of urine CTX-II (37). Although urine CTX-II was a significant predictor in our clinical model, it was not selected in our radiographic model. Urine CTX-II may therefore be a surrogate for radiographic factors, which could be useful in clinical practice when radiographs are unavailable.

A K/L grade of 1 and contralateral RKOA were strong predictors of RKOA in our radiographic model. These associations are already well-known (7,8), and an existing person-level prediction model also includes a K/L grade of 1 as a predictor (7).

This is the first time that hip α-angle has been identified as a predictor of incident RKOA. The α-angle is a radiologic measure used to diagnose femoroacetabular impingement at the hip, which causes hip pain and dysfunction (38). The most common threshold for diagnosis is an angle >50° (28). The mean of α-angles in the group with RKOA at year 5 exceeded this threshold in our study. A larger hip α-angle may thus reflect serious biomechanical changes and point to an OA origin beyond the knee that leads to an increased risk of knee RKOA. For example, a greater hip α-angle might indicate abnormal rotation of the tibia with respect to the femur, leading to knee OA (39). A greater hip α-angle may also be related to hip OA, which flexes, externally rotates, and adducts the hip. These changes may lead to apparent limb shortening.

We found higher BMD at the spine in women with short-term incident RKOA than in those without RKOA. A lumbar spine with a higher BMD has previously been associated with knee OA (40,41). A recent population-based study showed a correlation between the spine BMD and knee osteophyte score, and a negative correlation between the spine BMD and JSN (42). High systemic BMD has also been associated with incident RKOA (43,44), and an estimated 45% of the association between high bone mass and knee OA may be mediated by BMI (45). However, this is the first time that higher spine BMD has been shown to be useful in a predictive model of RKOA.

Clinical practice needs predictive tools for identifying those at risk of developing RKOA in the short term (6,46). Identifying those at short-term risk will allow new interventions targeting this population. However, 2 of the 3 previously developed models for incidence of RKOA followed individuals for 9 (7) and 12 (9) years. The studies therefore selected prognostic factors that could predict RKOA in the medium to long term. Riddle et al (8) investigated short-term risk by following participants for 5 years, but focused on older individuals with a higher BMI who were at high risk for developing OA, and only considered those with radiographic tibiofemoral OA. Our model bridges this gap by predicting the short-term incidence of all RKOA.

Unlike our study, none of the 3 previous studies (7–9) included any form of internal validation to account for optimism in the predictive performance of the developed models (25,47). The AUC values presented in these published studies would have been lower if internal validation were used.

Kerkhof et al (7) also produced a clinical model that excluded radiographic variables but included age, CTX-II, and BMI. This model had reasonable discriminatory power (AUC = 0.66). Our clinical model used knee-level quadriceps circumference instead of BMI and had improved discriminatory power (AUC = 0.69) than Kerkhof's clinical model. Both clinical models included urine CTX-II. The use of CTX-II added little to the predictive value of their model, whereas higher urine CTX-II levels doubled the probability of short-term RKOA in our clinical model (48). Our clinical model was also better at predicting incidence of RKOA than alternative models assessed by Kerkhof et al that considered ambulation, disability, and genetic risk factors.

Our clinical model performed similarly (AUC = 0.69) to the model of Zhang et al (9) when developed using data from the Nottingham knee OA retrospective cohort (AUC = 0.70). However, our clinical model is simpler to implement because it only considers 3 predictors (age, knee-level quadriceps circumference, and urine CTX-II), in comparison with their 6-predictor model (age, sex, BMI, occupational risk, family history of OA, and previous serious knee injury).

None of the existing models used calibration plots to check agreement between predicted and observed probabilities (7–9). Instead, they used the Hosmer-Lemeshow test. The TRIPOD guideline discourages using that test because it has limited statistical power when assessing poor calibration and tends to give a significant result if a large enough sample is used (25). We presented calibration plots showing that the confidence intervals for most of our models' predictions overlapped with the 45° line, showing agreement with the observed RKOA incidence. The probability of developing incident RKOA in the next 4 years in our general population of middle-aged women varied between 3 of 100 women and 20 of 100 women. Because this model was developed using data from a healthy, urban population of white middle-aged women, it cannot be assumed that the model will make accurate predictions in other populations. We suggest testing and validation before use in, for example, hospital inpatient, rural, younger female, older female, and male populations.

This study has several strengths. Our knee-level approach allowed us to identify risk factors whose effects are connected to the side of the body they are in, in relation to the knee that developed RKOA: quadriceps circumference, knee pain evaluated by the physician, specific knee K/L grade, contralateral knee with RKOA, and ipsilateral hip α-angle.

The reproducibility of the model was ensured by using multiple imputation and bootstrapping (49), so that only significant predictors were selected. We grouped the risk factors together into those that clinicians readily have access to and those that require radiography. The resulting 2 risk models support clinical decision-making between the physician and patient in 2 common scenarios, before and after radiography. We created a risk prediction tool to assess the short-term risk of incident RKOA, which will help physicians to inform their patients about their risk for incident RKOA and support the physician in addressing preventive measures to avoid the outcome.

The study also has potential limitations. Because uncontrolled parameters such as lifestyle factors may have changed since this study started in 1988 to 1989, the results may not be generalizable to individuals in 2018. However, our findings are consistent with recent studies (4,12,13,37), which support the idea that these potential differences may not have any impact on the relationship between the selected predictors and RKOA.

External validation was beyond the scope of this study, because an existing cohort of sufficient sample size containing the required predictors could not be found. Before the models are used in clinical practice, they should be externally validated using participant data from other than the Chingford study to test whether the model performance is overly optimistic. The models' generalizability in men, mixed-sex groups, and nonwhite populations should also be tested. The predictive capacity identified here may only apply to individuals with existing radiographic changes, which could limit the clinical utility of the tool. This requires further investigation.

K/L grade ≥2 does not account for knee symptoms. However, K/L grade ≥2 is strongly associated with knee pain and closely linked to knee replacement (32). We instead tested knee pain as a potential predictor, which was selected in the radiographic model.

We developed 2 predictive models for short-term incidence of RKOA in middle-aged, predominantly white women, a simple clinical model and a more complete radiographic model. The clinical model uses 3 variables that clinicians can easily measure and use to identify and inform women who have knees at higher risk of RKOA in the clinical setting: age, quadriceps circumference, and urine CTX-II level. The radiographic predictive model uses 7 variables and includes radiographic factors such as hip α-angle to increase the predictive capacity of the clinical model of short-term incidence of RKOA.

This is the first time that ipsilateral hip α-angle has been identified as a predictor of RKOA. The selection of hip α-angle, BMD at the lumbar spine, and contralateral knee OA as predictors of RKOA suggest OA origins beyond the knee area, although further research is needed before a mechanism for how these cause RKOA can be suggested. We also developed a risk score tool to help clinicians use the clinical model. Identifying women with knees at high risk of developing RKOA will enable preventive measures to be tested. Once externally validated, both models and the risk score tool could be useful in identifying participants for clinical trials.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Garriga had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Garriga, Sánchez-Santos, Cooper, Arden.

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REFERENCES

1. Cross M, Smith E, Hoy D, Nolte S, Ackerman I, Fransen M, et al. The global burden of hip and knee osteoarthritis: estimates from the Global Burden of Disease 2010 study. Ann Rheum Dis 2014;73:1323–30.
2. National Joint Registry. 14th annual report of the UK NJR. London: National Joint Registry for England, Wales and Northern Ireland; 2017.
3. Hart DJ, Doyle DV, Spector TD. Incidence and risk factors for radiographic knee osteoarthritis in middle-aged women: the Chingford Study. Arthritis Rheum 1999;42:17–24.
4. Jiang L, Tian W, Wang Y, Rong J, Bao C, Liu Y, et al. Body mass index and susceptibility to knee osteoarthritis: a systematic review and meta-analysis. Joint Bone Spine 2012;79:291–7.
5. Prieto-Alhambra D, Judge A, Javaid MK, Cooper C, Diez-Perez A, Arden NK. Incidence and risk factors for clinically diagnosed knee, hip and hand osteoarthritis: influences of age, gender and osteoarthritis affecting other joints. Ann Rheum Dis 2014;73:1659–64.
6. Conaghan PG, Kloppenburg M, Schett G, Bijlsma JW, EULAR Osteoarthritis Ad Hoc Committee. Osteoarthritis research priorities: a report from a EULAR ad hoc expert committee. Ann Rheum Dis 2014;73:1442–5.
7. Kerkhof HJ, Bierma-Zeinstra SM, Arden NK, Metrustry S, Castano-Betancourt M, Hart DJ, et al. Prediction model for knee osteoarthritis incidence, including clinical, genetic and biochemical risk factors. Ann Rheum Dis 2014;73:2116–21.
8. Riddle DL, Stratford PW, Perera RA. The incident tibiofemoral osteoarthritis with rapid progression phenotype: development and validation of a prognostic prediction rule. Osteoarthritis Cartilage 2016;24:2100–7.
9. Zhang W, McWilliams DF, Ingham SL, Doherty SA, Muthuri S, Muir KR, et al. Nottingham knee osteoarthritis risk prediction models. Ann Rheum Dis 2011;70:1599–604.
10. Leyland KM, Hart DJ, Javaid MK, Judge A, Kiran A, Soni A, et al. The natural history of radiographic knee osteoarthritis: a fourteen-year population-based cohort study. Arthritis Rheum 2012;64:2243–51.
11. Felson DT. Identifying different osteoarthritis phenotypes through epidemiology. Osteoarthritis Cartilage 2010;18:601–4.
12. Blagojevic M, Jinks C, Jeffery A, Jordan KP. Risk factors for onset of osteoarthritis of the knee in older adults: a systematic review and meta-analysis. Osteoarthritis Cartilage 2010;18:24–33.
13. Silverwood V, Blagojevic-Bucknall M, Jinks C, Jordan JL, Protheroe J, Jordan KP. Current evidence on risk factors for knee osteoarthritis in older adults: a systematic review and meta-analysis. Osteoarthritis Cartilage 2015;23:507–15.

14. Kellgren J, Lawrence J. Osteoarthritis and disk degeneration in an urban population. Ann Rheum Dis 1958;17:388–97.
15. Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. Ann Rheum Dis 1957;16:494–502.
16. Kellgren JH. The epidemiology of chronic rheumatism: atlas of standard radiographs of arthritis. 2nd ed. Philadelphia: Blackwell Scientific Publications; 1963.
17. Spector TD, Hart DJ, Byrne J, Harris PA, Dacre JE, Doyle DV. Definition of osteoarthritis of the knee for epidemiological studies. Ann Rheum Dis 1993;52:790–4.
18. Austin PC, Tu JV. Bootstrap methods for developing predictive models. Am Stat 2004;58:131–7.
19. Heymans MW, van Buuren S, Knol DL, van Mechelen W, de Vet HC. Variable selection under multiple imputation using the bootstrap in a prognostic study. BMC Med Res Methodol 2007;7:33.
20. Royston P, White IR. Multiple imputation by chained equations (MICE): implementation in Stata. J Stat Softw 2011;45.
21. Harrell FE Jr. Regression modeling strategies with applications to linear models, logistic regression, and survival analysis. New York: Springer; 2001.
22. Judge A, Arden NK, Batra RN, Thomas G, Beard D, Javaid MK, et al. The association of patient characteristics and surgical variables on symptoms of pain and function over 5 years following primary hip-replacement surgery: a prospective cohort study. BMJ Open 2013;3:pii:e002453.
23. Judge A, Javaid MK, Arden NK, Cushnaghan J, Reading I, Croft P, et al. Clinical tool to identify patients who are most likely to achieve long-term improvement in physical function after total hip arthroplasty. Arthritis Care Res (Hoboken) 2012;64:881–9.
24. Van Staa TP, Geusens P, Kanis JA, Leufkens HG, Gehlbach S, Cooper C. A simple clinical score for estimating the long-term risk of fracture in post-menopausal women. QJM 2006;99:673–82.
25. Moons KG, Altman DG, Reitsma JB, Ioannidis JP, Macaskill P, Steyerberg EW, et al. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): explanation and elaboration. Ann Intern Med 2015;162:W1–73.
26. Hassett G, Hart DJ, Manek NJ, Doyle DV, Spector TD. Risk factors for progression of lumbar spine disc degeneration: the Chingford Study. Arthritis Rheum 2003;48:3112–7.
27. Nicholls AS, Kiran A, Pollard TC, Hart DJ, Arden CP, Spector T, et al. The association between hip morphology parameters and nineteen-year risk of end-stage osteoarthritis of the hip: a nested case–control study. Arthritis Rheum 2011;63:3392–400.
28. Wright AA, Naze GS, Kavchak AE, Paul D, Kenison B, Hegedus EJ. Radiological variables associated with progression of femoroacetabular impingement of the hip: a systematic review. J Sci Med Sport 2015;18:122–7.
29. National Institute for Health and Clinical Excellence. Osteoarthritis: care and management in adults. London: National Institute for Health and Care Excellence; 2014.
30. Cooper C, Snow S, McAlindon TE, Kellingray S, Stuart B, Coggon D, et al. Risk factors for the incidence and progression of radiographic knee osteoarthritis. Arthritis Rheum 2000;43:995–1000.
31. Oliveria SA, Felson DT, Reed JI, Cirillo PA, Walker AM. Incidence of symptomatic hand, hip, and knee osteoarthritis among patients in a health maintenance organization. Arthritis Rheum 1995;38:1134–41.
32. Rogers MW, Wilder FV. The association of BMI and knee pain among persons with radiographic knee osteoarthritis: a cross-sectional study. BMC Musculoskelet Disord 2008;9:163.
33. Andriacchi TP, Favre J. The nature of in vivo mechanical signals that influence cartilage health and progression to knee osteoarthritis. Curr Rheumatol Rep 2014;16:463.
34. Wluka AE, Lombard CB, Cicuttini FM. Tackling obesity in knee osteoarthritis. Nat Rev Rheumatol 2012;9:225–35.
35. Man GS, Mologhianu G. Osteoarthritis pathogenesis: a complex process that involves the entire joint. J Med Life 2014;7:37–41.
36. Garnero P, Ayral X, Rousseau JC, Christgau S, Sandell LJ, Dougados M, et al. Uncoupling of type II collagen synthesis and degradation predicts progression of joint damage in patients with knee osteoarthritis. Arthritis Rheum 2002;46:2613–24.
37. Valdes AM, Meulenbelt I, Chassaing E, Arden NK, Bierma-Zeinstra S, Hart D, et al. Large scale meta-analysis of urinary C-terminal telopeptide, serum cartilage oligomeric protein and matrix metalloprotease degraded type II collagen and their role in prevalence, incidence and progression of osteoarthritis. Osteoarthritis Cartilage 2014;22:683–9.
38. Hack K, Di Primio G, Rakhra K, Beaulé PE. Prevalence of cam-type femoroacetabular impingement morphology in asymptomatic volunteers. J Bone Joint Surg Am 2010;92:2436–44.
39. Sharma L, Lou C, Felson DT, Dunlop DD, Kirwan-Mellis G, Hayes KW, et al. Laxity in healthy and osteoarthritic knees. Arthritis Rheum 1999;42:861–70.
40. Burger H, van Daele PL, Odding E, Valkenburg HA, Hofman A, Grobbee DE, et al. Association of radiographically evident osteoarthritis with higher bone mineral density and increased bone loss with age: the Rotterdam Study. Arthritis Rheum 1996;39:81–6.
41. Hart DJ, Cronin C, Daniels M, Worthy T, Doyle DV, Spector TD. The relationship of bone density and fracture to incident and progressive radiographic osteoarthritis of the knee: the Chingford Study. Arthritis Rheum 2002;46:92–9.
42. Wen L, Shin MH, Kang JH, Yim YR, Kim JE, Lee JW, et al. The relationships between bone mineral density and radiographic features of hand or knee osteoarthritis in older adults: data from the Dong-gu Study. Rheumatology (Oxford) 2016;55:495–503.
43. Bergink AP, Uitterlinden AG, Van Leeuwen JP, Hofman A, Verhaar JA, Pols HA. Bone mineral density and vertebral fracture history are associated with incident and progressive radiographic knee osteoarthritis in elderly men and women: the Rotterdam Study. Bone 2005;37:446–56.
44. Nevitt MC, Zhang Y, Javaid MK, Neogi T, Curtis JR, Niu J, et al. High systemic bone mineral density increases the risk of incident knee OA and joint space narrowing, but not radiographic progression of existing knee OA: the MOST study. Ann Rheum Dis 2010;69:163–8.
45. Hardcastle SA, Dieppe P, Gregson CL, Arden NK, Spector TD, Hart DJ, et al. Individuals with high bone mass have an increased prevalence of radiographic knee osteoarthritis. Bone 2015;71:171–9.
46. Felson DT, Zhang Y, Hannan MT, Naimark A, Weissman B, Aliabadi P, et al. Risk factors for incident radiographic knee osteoarthritis in the elderly: the Framingham Study. Arthritis Rheum 1997;40:728–33.
47. Steyerberg EW. Clinical prediction models: a practical approach to development, validation, and updating. Rotterdam: Springer Science & Business Media; 2008.
48. Odding E, Valkenburg HA, Algra D, Vandenouweland FA, Grobbee DE, Hofman A. Association of locomotor complaints and disability in the Rotterdam study. Ann Rheum Dis 1995;54:721–5.
49. Vergouwe Y, Royston P, Moons KG, Altman DG. Development and validation of a prediction model with missing predictor data: a practical approach. J Clin Epidemiol 2010;63:205–14.

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Association of Diabetes Mellitus and Biomarkers of Abnormal Glucose Metabolism With Incident Radiographic Knee Osteoarthritis

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Objective. The association of diabetes mellitus (DM) with increased risk of knee osteoarthritis (OA) is uncertain. We evaluated associations of DM and biomarkers of abnormal glucose metabolism with incident radiographic knee OA, controlling for body mass index (BMI).

Methods. Participants (mean ± SD age 60.6 ± 7.8 years; mean ± SD body mass index [BMI] 29.1 ± 4.9 kg/m^2) were from the Multicenter Osteoarthritis Study and did not have radiographic knee OA at baseline (Kellgren/Lawrence [K/L] grade <2 bilaterally). A random sample (n = 987) was selected and stratified by BMI. Baseline serum fasting glucose and homeostasis model assessment–estimated insulin resistance (HOMA-IR) were measured. Participants were categorized as having DM based on self-report, use of medication, or fasting glucose ≥126 mg/dl. Incident radiographic knee OA (K/L grade ≥2 or knee replacement) was assessed at 3 follow-up visits (30, 60, and 84 months). Knee-level pooled logistic regression analysis was performed to obtain odds ratios (ORs) (95% confidence interval [95% CI]) for associations of DM status and biomarkers of abnormal glucose metabolism with incident radiographic knee OA.

Results. After adjustment for BMI, the odds of incident radiographic knee OA were not associated with baseline DM status nor with levels of fasting glucose and HOMA-IR, overall and in men. In women, HOMA-IR was inversely associated with odds of incident radiographic knee OA (adjusted OR 0.80 [95% CI 0.69–0.94], $P = 0.005$).

Conclusion. DM and higher levels of biomarkers of abnormal glucose metabolism were not associated with increased odds of incident radiographic knee OA after adjusting for BMI in this cohort overall. A possible protective association of higher HOMA-IR with incident radiographic knee OA in women warrants further investigation.

INTRODUCTION

Osteoarthritis (OA) and diabetes mellitus (DM) are common among older adults in the US. Knee OA causes structural changes in the joint, resulting in pain and stiffness, and is a prominent cause of global disability (1). It is estimated that 16% of adults in the US who are ages 45 years and older develop symptomatic knee OA (2,3). By 2018, the prevalence of knee OA is projected to reach 35% in obese individuals ages 60–64 years (4). In the US, approximately 9.3% of the population has DM, and DM is even more prevalent among older adults (25.9% of adults ages 65 years and older) (5). Moreover, by 2050, 55% of adults in this age group are expected to be diagnosed with DM. Type 2 DM is more common and comprises 90–95% of all DM cases (6).

Findings from previous epidemiologic studies have suggested that OA is associated with elevated fasting glucose (7,8) and is highly prevalent among those with DM (9–13). Proposed etiologies include advanced glycation end products, which reduce cartilage integrity (14,15). Additionally, inflammation could contribute to changes in cartilage metabolism and integrity (14), as well as neuromuscular impairment (as a result of symmetric sensory polyneuropathy and autonomic neuropathy from long-standing DM), which could lead to muscle weakness and joint laxity (15).

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No potential conflicts of interest relevant to this article were reported.

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SIGNIFICANCE & INNOVATIONS

- Osteoarthritis (OA) and diabetes mellitus (DM) are 2 of the most prevalent diseases worldwide.
- Findings of meta-analyses have suggested positive associations of DM and OA, though limitations of previous studies include heterogeneity in definitions of OA and DM and lack of adjustment for body mass index (BMI) in some studies. In this prospective study, we examined associations of DM status and biomarkers of abnormal glucose metabolism specifically with incident radiographic knee OA.
- Among older women and men with a high risk of developing knee OA, DM and biomarkers of abnormal glucose metabolism were not associated with odds of incident radiographic knee OA after adjustment for BMI.
- A possible protective association in women of greater insulin resistance (homeostasis model assessment–estimated insulin resistance) with lower odds of incident radiographic knee OA (after BMI adjustment) deserves further investigation.

There are, however, few studies specifically of the association of DM and knee OA, and results have been conflicting (16,17). Some studies of DM and knee OA have not adjusted for body mass index (BMI), even though obesity (high BMI) increases mechanical load on the knee and is a strong risk factor for both DM and OA (16–20). A meta-analysis of 6 studies demonstrated an increased risk of knee OA in persons with DM, but a majority of these studies did not adjust for BMI or obesity (17). A second meta-analysis of 7 studies that adjusted for BMI showed a small, but significant, increase in risk of OA, but this analysis pooled results from studies of knee, hip, and hand OA (16). In addition, both meta-analyses pooled results from cross-sectional and prospective studies and included studies with joint replacement as the outcome, so the temporal relationship between DM and OA is uncertain (16,17). The potential for reverse causality in cross-sectional studies (i.e., OA contributing to an increased risk of DM) has been shown (17,21), indicating that prospective studies of the association of DM and abnormalities of glucose metabolism with the subsequent development of OA are needed to understand the contribution of DM to the risk of OA. One prospective study (22) demonstrated an increased subsequent risk of either knee or hip replacement (a surrogate for severe OA) in patients with DM after adjusting for BMI. It remains unknown whether the presence of DM precedes development of OA when arthroplasty is the outcome.

The finding of an association between DM and OA after adjustment for BMI in some studies suggests that other aspects of DM, including metabolic abnormalities, may contribute to the risk of OA development. However, prospective studies have not found an association between hyperglycemia and either the risk of hip or knee replacement (23) or the risk of incident knee OA (24) after adjustment for BMI. A recent systematic review of abnormal glucose metabolism as a risk factor for OA showed that, of 5 longitudinal studies related to knee OA that adjusted for obesity, 3 studies reported no association, 1 reported a decrease in OA risk, and 1 reported an increase in OA risk (25). Additional prospective studies of DM and abnormalities of glucose metabolism are needed to fully elucidate their potential role in the development of OA in specific joints.

In light of these previous reports, we evaluated the association of DM and of biomarkers of abnormal glucose metabolism with incident radiographic knee osteoarthritis (radiographic knee OA) of the tibiofemoral joint among participants in the Multicenter Osteoarthritis Study (MOST). We hypothesized that the presence of DM, as well as hyperglycemia and elevated insulin resistance in participants with and without DM, would be associated with increased odds of incident radiographic knee OA, independent of BMI.

MATERIALS AND METHODS

Study participants. We utilized data from MOST, which is a National Institutes of Health (NIH)–funded, community-based longitudinal cohort study of risk factors for knee OA in 3,026 men and women ages 50–79 years, with or at high risk for knee OA. Eligibility for MOST included being overweight or obese (defined as weighing more than the medium weight for age- and sex-specific group included in the risk factors for CVD identified in the Framingham Heart Study), history of knee injury that made it difficult to walk for at least 1 week, prior knee surgery, or frequent knee pain (26,27). The MOST clinical centers are located at the University of Alabama at Birmingham and the University of Iowa; participants were recruited from the surrounding areas. Subjects with bilateral total knee replacement (TKR), those unable to walk without assistance or who were unlikely to participate in follow-up examinations at baseline were excluded from MOST. Weight-bearing posteroanterior and lateral knee radiographs were acquired during baseline, 30-, 60-, and 84-month clinic visits. In compliance with the Helsinki Declaration, the protocol for the MOST Study was approved by institutional review boards at Boston University, the University of Iowa, the University of Alabama at Birmingham, and the University of California, San Francisco.

Sample selection. To be eligible for the present analysis, MOST participants had to have 2 native knees free of OA at baseline (Kellgren/Lawrence [K/L] grade 0 or 1 in native knees and no knee replacement), knee radiographs at baseline and ≥1 follow-up visit, and archived baseline fasting serum available. Because of a limited budget for assays, we were unable to include all eligible participants (n = 1,280). We therefore selected a random sample of 1,000 from the eligible participants. The sample was stratified by decile of BMI (i.e., 100 participants [58 women and 42 men] were randomly selected from each decile of BMI). We stratified on

BMI because control for this variable is essential to determine if DM is associated with OA, independent of BMI. As other studies have shown (28,29), residual bias can occur if relationships with a continuous confounder are not properly modeled and a linear relationship is incorrectly assumed. Strategies to deal with nonlinear relationships, which are not uncommon in epidemiologic studies of exposure-outcome associations, include ensuring that the data are spread across a wide range, as well as the use of restricted splines. Our sampling approach therefore resulted in a more even distribution of BMI across the entire range of values, which increases the precision of the adjusted ORs but does not add bias to the estimates of association. Our approach also allowed us to better estimate the shape of the relationship of BMI with exposure and outcome using splines, with the goal of increased accuracy and precision of the BMI adjusted ORs. However, we found that the use of splines did not change the adjusted results, so we did not use splines in the main analyses. The BMI groups (deciles) were used only for the selection of participants. Of these 1,000 participants, 13 were excluded after we determined that they were insulin users at baseline. The final sample size for the present analysis was 987 (Figure 1).

Measurements. Participants were categorized as having DM at baseline based on the presence of at least 1 of the following: self-reported diagnosis of DM ("Do you have diabetes or high blood sugar?"), use of antidiabetic medications (e.g., meglitinides, metformin, sulfonylureas, thiazolidinediones) determined by review of all prescription medications taken in the past 30 days, or a fasting glucose of ≥126 mg/dl.

Weight (kg) and height (mm) were measured by standard medical beam balance and wall-mounted Harpenden stadiometer (Holtain), respectively (30). Weight and height measurements

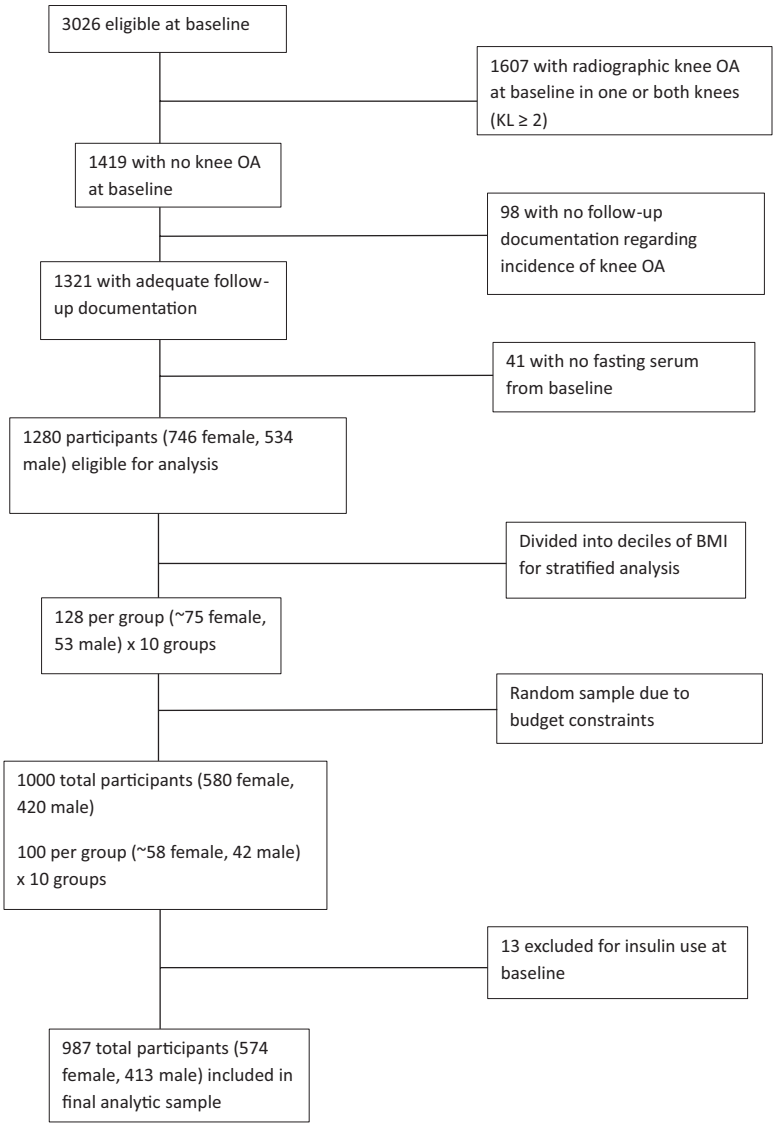

Figure 1. Flow chart of study sample selection. K/L = Kellgren/Lawrence; OA = osteoarthritis; BMI = body mass index.

were used to calculate BMI (kg/m^2). Self-reported health status was determined via the Short Form 12 Health Survey (26). Self-reported physical activity was assessed at baseline with the Physical Activity Scale for the Elderly (PASE) (31).

Fasting glucose (Unical DxC 800 auto-analyzer, Beckman Coulter) and free insulin (Abbott Architect i1000SR immunoassay analyzer, Abbot Diagnostics) levels at baseline were measured on all subjects. Coefficients of variation ranged from 1.4% to 5.6% and 2.4% to 2.9%, respectively. Insulin resistance was determined with the homeostasis model assessment–estimated insulin resistance (HOMA-IR) formula, which is calculated as: (fasting glucose concentration [mg/dl] × fasting insulin concentration [μU/ml])/405. HOMA-IR values have been validated as surrogate markers of insulin resistance and correlate well with insulin resistance values determined by euglycemic-insulin clamp or the frequently sampled intravenous glucose tolerance test (32).

Posteroanterior weight-bearing knee radiographs were obtained using a Synaflexer frame (Synarc) to create a standardized knee position. All radiographs for each participant were read together in known order by a team of experienced readers at a central location (Boston University). Readers were blind to the DM status and all clinical characteristics of the participants. Each of the 2 readers read all radiographs from all the participants. Cases of disagreement were addressed by adjudication with a third reader (33,34). Self-reported knee replacement was confirmed by radiographs and/or medical records. For the purposes of this knee-level investigation, knees with incident tibiofemoral radiographic knee OA were identified separately at each visit from baseline to 84 months. A knee was defined as having this end point if there was at least 1 follow-up radiograph showing radiographic knee OA (K/L grade ≥2) or if there had been a TKR at the time of the visit. The status of every knee was followed from baseline to 84 months. Once the criteria for incident radiographic knee OA were met, the knee was considered to have radiographic knee OA for the remainder of the study. Additionally, physical examinations of joints occurred at baseline and 30-month follow-up (26).

Statistical analysis. Descriptive characteristics were analyzed by analysis of variance for continuous variables and chi-squared test for categorical variables. Incidence of radiographic knee OA between baseline and the 84-month follow-up were evaluated as cumulative incidence.

In this study, events were discovered at clinic visits when knee radiographs were acquired, and we used pooled logistic regression to conduct a discrete time survival analysis (consecutive clinic visit at 30, 60, or 84 months). To conduct such an analysis, the data were transformed to multiple records per knee, 1 record per visit. If knee status was unknown (e.g., if the visit was missed or if the visit was done without imaging), the outcome was considered to be missing. Once an event occurred, all subsequent records (visits) for the affected knee were dropped from the analysis (i.e., each incidence was counted only once). Data collection continued for the other knee.

Knee-level pooled logistic regression analysis (35,36) was performed to obtain ORs and 95% CIs for incidence of radiographic knee OA predicted by baseline DM status, baseline fasting glucose, and HOMA-IR. Generalized estimating equations were used to account for within-person correlations (between knees). Models were adjusted for age, sex, race, clinic site, visit (time to event; this variable allowed for the rate of events to change over time), and time-dependent BMI at each visit. Formal interactions for exposure × sex, as well as exposure × BMI, were examined. Missing observations (2.4% in this study) were dropped from the analysis.

Sensitivity analyses were also performed. We first examined whether exclusion of participants with newly reported DM (n = 54) would influence the results of the analyses. Secondly, we performed the analyses in whites only (n = 849) in order to remove the influence of the race. Additionally, we ran further sensitivity analyses using time-dependent DM (a combination of baseline DM and incident self-report of DM at a subsequent visit) and DM medication use, and specifically metformin use, as primary exposures. We also adjusted models for metformin use (i.e., in this sensitivity analysis, metformin use was a covariate rather than a primary exposure). Lastly, we examined the effect of physical activity by adjusting models for PASE score. All analyses were performed using SAS, version 9.4.

RESULTS

Among the 987 participants (mean ± SD age 60.6 ± 7.8 years, 58% female, mean ± SD BMI 29.1 ± 4.9 kg/m^2), 94 (9.5%) had DM at baseline. Compared to participants without DM, participants with DM were more likely to be male, nonwhite, and reside in Alabama. Among whites residing in Iowa, the prevalence of DM was 7.1% (5.8% in women and 9.0% in men). Among whites in Alabama, the prevalence of DM was 8.4% (7.2% in women and 10.1% in men). The prevalence of DM in African American participants who resided in Alabama was 23.3% (16.7% in women and 31.5% in men). There were only 3 African American participants who resided in Iowa; all were men and none had DM.

Of the 94 participants classified as having DM at baseline, 56 were taking DM medications (including 42 taking metformin), and 56 had elevated fasting glucose. Nineteen participants were classified as having DM based on self-report only, 2 had DM based on medications only, and 19 had DM based on fasting glucose levels only.

As expected, participants with DM had significantly higher fasting glucose, fasting insulin, and HOMA-IR compared to participants without DM at baseline (Table 1). Additionally, participants with DM had a higher BMI and were less likely to consider

Table 1. Descriptive characteristics at baseline*

	No baseline DM (n = 893)	Baseline DM (n = 94)	*P*
Demographic characteristics			
Age, years	60.6 ± 7.8	60.7 ± 8.0	0.877
Women, no. (%)	531 (59.5)	43 (45.7)	0.010†
White race, no. (%)	784 (87.8)	65 (69.1)	<0.0001†
Clinic (UAB), no. (%)	425 (47.6)	59 (62.8)	0.005†
Metabolic parameters			
Fasting blood glucose (mg/dl)	95.4 ± 9.2	141.7 ± 45.9	<0.0001†
Fasting insulin (mcIU/ml)	9.0 ± 7.6	14.6 ± 10.2	<0.0001†
HOMA-IR	2.2 ± 1.9	5.0 ± 3.7	<0.0001†
Anthropometric characteristics			
Weight (kg)	83.0 ± 15.8	95.9 ± 19.0	<0.0001†
Height (m)	1.7 ± 0.08	1.7 ± 0.09	0.1105
BMI (kg/m^2)	28.7 ± 4.7	32.5 ± 5.2	<0.0001†
General functional status			
Health status (self-assessment)			
Excellent/very good/good, no. (%)	840 (94.1)	73 (77.7)	<0.0001†
Fair/poor, no. (%)	53 (5.9)	21 (22.3)	
PASE (activity score)	181.5 ± 89.3	197.2 ± 98.3	0.1088

* Values are the mean ± SD unless indicated otherwise. DM = diabetes mellitus; UAB = University of Alabama at Birmingham; HOMA-IR = homeostasis model assessment–estimated insulin resistance; BMI = body mass index; PASE = Physical Activity Scale for the Elderly.
† Significant.

their health status to be "excellent," "very good," or "good" compared to participants without DM (Table 1).

In the cohort of 987 participants, 1,972 knees were included in this analysis. Two participants did not return for follow-up visits, but they reported by telephone contact a knee replacement between the 60-month and 84-month visits. There were 165 (2.4%) records with a missing interim visit, and there were 365 knees (18%) that did not have 84 months of follow-up.

There were 409 knees with incident radiographic knee OA. Between baseline and the 84-month follow-up visit, the cumulative incidence of radiographic knee OA for all knees was 23.3%; the cumulative incidence was slightly higher for knees of patients with DM compared to knees of those without DM (24.0% versus 23.2%; Table 2).

The ORs of incident radiographic knee OA by baseline DM status, baseline fasting glucose, and HOMA-IR are presented in Table 3. Baseline fasting glucose and HOMA-IR were associated with increased odds of incident radiographic knee OA in the unadjusted model, as well as in the model adjusted for age, race, clinic site, and visit. After adjustment for BMI, these associations were attenuated and lost statistical significance. Fasting insulin values were highly correlated with HOMA-IR by design. As expected, the risk of incident radiographic knee OA by fasting insulin mirrored the results for HOMA-IR and did not reveal any new findings (data not shown).

The only formal interaction that neared significance ($P < 0.05$) was between HOMA-IR and sex ($P = 0.12$); sex-stratified results for the OR for HOMA-IR and incident radiographic knee OA are presented in Table 4. In women, elevated HOMA-IR was associated with lower odds of incident radiographic knee OA in the model adjusted for sex, age, race, clinic site, visit, and BMI. In men, elevated HOMA-IR was associated with increased odds for radiographic knee OA in the model adjusted for sex, age, race, clinic site, and visit. However, after adjustment for BMI, this association was attenuated and was no longer statistically significant.

We repeated all analyses using participant-level incidence of radiographic knee OA as the outcome. There were no noteworthy differences between results at the participant level and results at the knee level (data not shown). A total of 54 participants self-reported a diagnosis of DM between

Table 2. Knee-level incidence of radiographic knee OA during 84-month follow-up*

	Study sample (n = 1,972 knees)	No baseline DM (n = 1,785 knees)	Baseline DM (n = 187 knees)
No. of knees with incident Radiographic knee OA	409	368	41
Cumulative incidence (%)			
At 30 months	6.5	6.4	8.0
At 60 months	17.2	17.1	17.5
At 84 months	23.3	23.2	24.0

* OA = osteoarthritis; DM = diabetes mellitus.

Table 3. Odds ratios for incidence of knee OA (n = 987 participants [1,972 knees])*

Model	Exposure	Unadjusted model	Adjusted model†	Adjusted model‡
1	Baseline DM status	1.06 (0.72–1.54), 0.778	1.05 (0.71–1.54), 0.813	0.79 (0.53–1.18), 0.246
2	Fasting glucose (per 1 SD)	1.14 (1.02–1.28), 0.021§	1.14 (1.01–1.27), 0.031§	0.98 (0.87–1.11), 0.751
3	HOMA-IR (per 1 SD)	1.13 (1.01–1.27), 0.033§	1.13 (1.00–1.27), 0.042§	0.89 (0.79–1.01), 0.077

* Values are the odds ratio (95% confidence interval), *P* value for incidence of knee osteoarthritis (OA). DM = diabetes mellitus; HOMA-IR = homeostasis model of assessment– insulin resistance.
† Adjusted for sex, age, race, clinic site, and visit.
‡ Adjusted for sex, age, race, clinic site, visit, and body mass index (time-dependent).
§ Significant.

baseline and the 84-month follow-up visit, but excluding these participants from the non-DM group did not substantially change overall results (see Supplementary Table 1, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23809/abstract). Among white participants overall, there were no associations between baseline DM status, fasting glucose, or HOMA-IR and odds of incident radiographic knee OA in any of the models (see Supplementary Table 2, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.23809/abstract). Sensitivity analyses using time-dependent DM as the exposure and PASE score as a covariate did not substantially alter our main findings (data not shown). Metformin usage by itself was associated with a nonsignificant protective effect (OR 0.69 [95% CI 0.43–1.09], $P = 0.11$) for radiographic knee OA, but when included as a covariate in models with HOMA-IR, the protective effect of the HOMA-IR in women was unchanged and remained significant ($P = 0.007$).

DISCUSSION

This prospective analysis among older women and men with an elevated risk of developing knee OA contributes to the literature by focusing specifically on the associations between DM status (as defined by self-report, use of antidiabetic medications, or fasting glucose) and biomarkers of abnormal glucose metabolism, with odds of subsequently developing incident radiographic knee OA. Contrary to our hypothesis, after adjustment for BMI (a strong risk factor for both DM and knee OA) (16–20) we did not find increased odds of incident radiographic knee OA in participants with DM nor in participants with higher baseline levels of fasting glucose and HOMA-IR. Surprisingly, after adjustment for BMI, we observed a protective association of higher levels of HOMA-IR with the odds of incident radiographic knee OA in women. This protective effect was not explained by use of diabetic medications in those with insulin resistance.

Table 4. Odds ratios for incidence of knee OA by HOMA-IR*

Sex	Unadjusted model	Adjusted model†	Adjusted model‡
Women§	1.08 (0.94–1.24), 0.303	1.05 (0.91–1.22), 0.470	0.80 (0.69–0.94), 0.005¶
Men#	1.28 (1.05–1.56), 0.015¶	1.30 (1.07–1.58), 0.007¶	1.09 (0.89–1.33), 0.424

* Values are the odds ratio (95% confidence interval), *P* value for incidence of knee osteoarthritis (OA). HOMA-IR = homeostasis model assessment–estimated insulin resistance.
† Adjusted for sex, age, race, clinic site, and visit.
‡ Adjusted for sex, age, race, clinic site, visit, and body mass index (time-dependent).
§ n = 574.
¶ Significant.
# n = 413.

Our findings contrast with some previous studies of DM and DM-related factors and knee OA but are consistent with other studies. At least 2 meta-analyses have suggested an overall positive, though modest, association between the presence of DM and OA (16,17). However, these analyses have important limitations, which include combining studies of knee, hip, and hand joints, combining studies using different definitions of OA (radiographic, arthroplasty, and clinical diagnosis) and pooling results from cross-sectional and prospective studies. Many of the included studies were cross-sectional and/or did not adjust for obesity (16,17), a strong risk factor for both DM and knee OA (18–20) and important potential confounding factor. To our knowledge, there are few prospective studies of DM and knee OA outcomes, and none of incident radiographic knee OA, the focus of the present study. A recent prospective study (13) found, after BMI adjustment, that increased radiographic progression of existing knee OA was associated with baseline DM in men, but not women. Whether DM preceded the onset of knee OA in this study is not known.

Several cohort studies have explored associations between DM-related variables, including metabolic factors, and knee OA (22,37–39). Yoshimura and colleagues analyzed impaired glucose tolerance (IGT), based on elevated glycosylated hemoglobin A_{1c}, and the 3-year incidence and progression of radiographic knee OA in a cohort of Japanese men and women. They found that IGT was associated with an increased incidence of radiographic knee OA, but not with the progression of radiographic knee OA, after adjusting for obesity and other components of the metabolic syndrome (37). In contrast, in a recent study of components of metabolic syndrome and the incidence of both radiographic knee OA and symptomatic knee OA, Niu et al found no association between elevated fasting glucose and these knee OA outcomes (24). Similarly, in 2 prospective studies with knee replacement as the outcome, after adjustment for BMI, there was no association between elevated fasting glucose and knee OA (23,38). The findings of the present analysis, along with the conflicting reports in the literature, illustrate the complexity of determining whether

an independent relationship between DM and OA exists after accounting for the potentially confounding role of obesity.

Our observation of an inverse association between HOMA-IR and odds of radiographic knee OA incidence in women was unexpected and possibly spurious but was not explained by use of diabetic medications, or metformin in particular, in those with insulin resistance. We also observed a potential, though not significant, protective effect of metformin usage on incident radiographic knee OA. This aligns with recent reports (39–41). Further investigation of potential protective effects of DM and DM medications is warranted.

The association of obesity and DM with OA has suggested the existence of a metabolic syndrome-associated OA phenotype, with potential etiologic roles in joint damage for a variety of systemic and local metabolic abnormalities, including impaired glucose metabolism, hypertension, dyslipidemia, inflammation, oxidative stress, and advanced glycation end products (15,42). Future studies should address associations of DM and OA within the broader context of metabolic OA phenotypes.

This study has several strengths, including the utilization of a prospective design to study incident radiographic knee OA while eliminating the potential for reverse causality, a well-characterized, community-acquired cohort, and repeated follow-up over 84 months for development of radiographic knee OA. We did not rely solely on self-report to identify participants with DM but also based DM status on use of prescription antidiabetic medications and fasting glucose levels.

Our study also has several limitations. It is possible that some participants may have given unreliable information about fasting (e.g., overstating the number of hours they had been fasting before the blood draw) and could have been falsely classified as having DM due to elevated glucose levels. Since the study is prospective, this type of misclassification is likely to be nondifferential with respect to incident OA, which could influence the ORs toward the null (i.e., no association). Data on DM type were not collected in the present study. It is likely that the majority of participants with DM in the present analysis had type 2 DM since type 2 DM is more prevalent (6) and insulin users were excluded; however, it is possible that some participants had type 1 DM. The definition of knee OA in this study was based on radiographic findings only (43). Because our sample included only those without radiographic OA at baseline, there were just 14 knees with incident symptomatic OA (the combination of radiographic OA and frequent knee pain), which is too few for a separate analysis. Results may differ for incident symptomatic OA.

Furthermore, this analysis was limited to tibiofemoral OA; findings may differ when taking patellofermoral or whole knee OA into account. DM has also been associated with reduced levels of osteophyte formation, possibly due to diminished availability of insulin at the cellular level or diabetic microvascular disease attenuating proliferation (44). Potential protective effects on radiographic knee OA incidence in this study may reflect the importance of osteophytes in radiographic definitions of OA. Additionally, the MOST cohort was selected to have an elevated risk for incident radiographic knee OA and had a high BMI at baseline (6). Thus, results of the present study may have limited generalizability since our study population does not reflect the incidence of radiographic knee OA or prevalence of DM in the general population. Finally, it is possible that our sample size was too small to detect associations between the exposure variables and radiographic knee OA; in particular, the wide CIs for the baseline DM models in Table 3 suggest a certain degree of imprecision.

In this cohort of older adults with a high risk of developing knee OA, DM, and higher levels of biomarkers of abnormal glucose metabolism were not associated with increased odds of incident radiographic knee OA after adjusting for BMI. We found evidence suggesting that these associations may differ by sex. In particular, a protective association of higher levels of insulin resistance (HOMA-IR) with odds of incident radiographic knee OA after BMI adjustment in women, but not men, deserves further investigation.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Rogers-Soeder had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design. Lane, Walimbe, Schwartz.

Acquisition of data. Lewis, Segal.

Analysis and interpretation of data. Rogers-Soeder, Lane, Walimbe, Schwartz, Tolstykh, Felson, Nevitt.

REFERENCES

1. Cross M, Smith E, Hoy D, Nolte S, Ackerman I, Fransen M, et al. The global burden of hip and knee osteoarthritis: estimates from the global burden of disease 2010 study. Ann Rheum Dis 2014;73:1323–30.
2. Jordan JM, Helmick CG, Renner JB, Luta G, Dragomir AD, Woodard J, et al. Prevalence of knee symptoms and radiographic and symptomatic knee osteoarthritis in African Americans and Caucasians: the Johnston County Osteoarthritis Project. J Rheumatol 2007;34:172–80.
3. Kotlarz H, Gunnarsson CL, Fang H, Rizzo JA. Insurer and out-of-pocket costs of osteoarthritis in the US: evidence from national survey data. Arthritis Rheum 2009;60:3546–53.
4. Holt HL, Katz JN, Reichmann WM, Gerlovin H, Wright EA, Hunter DJ, et al. Forecasting the burden of advanced knee osteoarthritis over a 10-year period in a cohort of 60-64 year-old US adults. Osteoarthritis Cartilage 2011;19:44–50.
5. Centers for Disease Control and Prevention. National diabetes statistics report, 2014. URL: https://www.cdc.gov/diabetes/pdfs/

data/2014-report-estimates-of-diabetes-and-its-burden-in-the-united-states.pdf.

6. Caspersen CJ, Thomas GD, Boseman LA, Beckles GL, Albright AL. Aging, diabetes, and the public health system in the United States. Am J Public Health 2012;102:1482–97.
7. Cimmino MA, Cutolo M. Plasma glucose concentration in symptomatic osteoarthritis: a clinical and epidemiological survey. Clin Exp Rheumatol 1990;8:251–7.
8. Hart DJ, Doyle DV, Spector TD. Association between metabolic factors and knee osteoarthritis in women: the Chingford Study. J Rheumatol 1995;22:1118–23.
9. Waine H, Nevinny D, Rosenthal J, Joffe IB. Association of osteoarthritis and diabetes mellitus. Tufts Folia Med 1961;7:13–9.
10. Sturmer T, Brenner H, Brenner RE, Gunther KP. Non-insulin dependent diabetes mellitus (NIDDM) and patterns of osteoarthritis: the Ulm osteoarthritis study. Scand J Rheumatol 2001;30:169–71.
11. Cheng YJ, Imperatore G, Caspersen CJ, Gregg EW, Albright AL, Helmick CG. Prevalence of diagnosed arthritis and arthritis-attributable activity limitation among adults with and without diagnosed diabetes: United States, 2008–2010. Diabetes Care 2012;35:1686–91.
12. Chanchek N, Gersing AS, Schwaiger BJ, Nevitt MC, Neumann J, Joseph GB, et al. Association of diabetes mellitus and biochemical knee cartilage composition assessed by T2 relaxation time measurements: data from the osteoarthritis initiative. J Magn Reson Imaging 2018;47:380–90.
13. Eymard F, Parsons C, Edwards MH, Petit-Dop F, Reginster JY, Bruyere O, et al. Diabetes is a risk factor for knee osteoarthritis progression. Osteoarthritis Cartilage 2015;23:851–9.
14. Laiguillon MC, Courties A, Houard X, Auclair M, Sautet A, Capeau J, et al. Characterization of diabetic osteoarthritic cartilage and role of high glucose environment on chondrocyte activation: toward pathophysiological delineation of diabetes mellitus-related osteoarthritis. Osteoarthritis Cartilage 2015;23:1513–22.
15. Berenbaum F. Diabetes-induced osteoarthritis: from a new paradigm to a new phenotype. Ann Rheum Dis 2011;70:1354–6.
16. Williams MF, London DA, Husni EM, Navaneethan S, Kashyap SR. Type 2 diabetes and osteoarthritis: a systematic review and meta-analysis. J Diabetes Complications 2016;30:944–50.
17. Louati K, Vidal C, Berenbaum F, Sellam J. Association between diabetes mellitus and osteoarthritis: systematic literature review and meta-analysis. RMD Open 2015;1:e000077.
18. Lee R, Kean WF. Obesity and knee osteoarthritis. Inflammopharmacology 2012;20:53–8.
19. Gray N, Picone G, Sloan F, Yashkin A. Relation between BMI and diabetes mellitus and its complications among US older adults. South Med J 2015;108:29–36.
20. Crawford AG, Cote C, Couto J, Daskiran M, Gunnarsson C, Haas K, et al. Prevalence of obesity, type II diabetes mellitus, hyperlipidemia, and hypertension in the United States: findings from the GE Centricity Electronic Medical Record database. Popul Health Manag 2010;13:151–61.
21. Rahman MM, Cibere J, Anis AH, Goldsmith CH, Kopec JA. Risk of type 2 diabetes among osteoarthritis patients in a prospective longitudinal study. Int J Rheumatol 2014;2014:620920.
22. Schett G, Kleyer A, Perricone C, Sahinbegovic E, Iagnocco A, Zwerina J, et al. Diabetes is an independent predictor for severe osteoarthritis: results from a longitudinal cohort study. Diabetes Care 2013;36:403–9.
23. Engstrom G, Gerhardsson de Verdier M, Rollof J, Nilsson PM, Lohmander LS. C-reactive protein, metabolic syndrome and incidence of severe hip and knee osteoarthritis: a population-based cohort study. Osteoarthritis Cartilage 2009;17:168–73.
24. Niu J, Clancy M, Aliabadi P, Vasan R, Felson DT. Metabolic syndrome, its components, and knee osteoarthritis: the Framingham Osteoarthritis Study. Arthritis Rheumatol 2017;69:1194–203.
25. Dawson LP, Fairley JL, Papandony MC, Hussain SM, Cicuttini FM, Wluka AE. Is abnormal glucose tolerance or diabetes a risk factor for knee, hip, or hand osteoarthritis? A systematic review. Semin Arthritis Rheum 2018;48:176–89.
26. Segal NA, Nevitt MC, Gross KD, Hietpas J, Glass NA, Lewis CE, et al. The Multicenter Osteoarthritis Study: opportunities for rehabilitation research. PM R 2013;5:647–54.
27. Segal NA, Torner JC, Felson DT, Niu J, Sharma L, Lewis CE, et al. Knee extensor strength does not protect against incident knee symptoms at 30 months in the multicenter knee osteoarthritis (MOST) cohort. PM R 2009;1:459–65.
28. Groenwold RH, Klungel OH, Altman DG, van der Graaf Y, Hoes AW, Moons KG. Adjustment for continuous confounders: an example of how to prevent residual confounding. Cmaj 2013;185:401–6.
29. May S, Bigelow C. Modeling nonlinear dose-response relationships in epidemiologic studies: statistical approaches and practical challenges. Dose Response 2006;3:474–90.
30. Segal NA, Felson DT, Torner JC, Zhu Y, Curtis JR, Niu J, et al. Greater trochanteric pain syndrome: epidemiology and associated factors. Arch Phys Med Rehabil 2007;88:988–92.
31. Washburn RA, Smith KW, Jette AM, Janney CA. The Physical Activity Scale for the Elderly (PASE): development and evaluation. J Clin Epidemiol 1993;46:153–62.
32. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28:412–9.
33. Felson DT, Nevitt MC, Yang M, Clancy M, Niu J, Torner JC, et al. A new approach yields high rates of radiographic progression in knee osteoarthritis. J Rheumatol 2008;35:2047–54.
34. Felson DT, Niu J, Yang T, Torner J, Lewis CE, Aliabadi P, et al. Physical activity, alignment and knee osteoarthritis: data from MOST and the OAI. Osteoarthritis Cartilage 2013;21:789–95.
35. Horton DB, Haynes K, Denburg MR, Thacker MM, Rose CD, Putt ME, et al. Oral glucocorticoid use and osteonecrosis in children and adults with chronic inflammatory diseases: a population-based cohort study. BMJ Open 2017;7:e016788.
36. D'Agostino RB, Lee ML, Belanger AJ, Cupples LA, Anderson K, Kannel WB. Relation of pooled logistic regression to time dependent Cox regression analysis: the Framingham Heart Study. Stat Med 1990;9:1501–15.
37. Yoshimura N, Muraki S, Oka H, Tanaka S, Kawaguchi H, Nakamura K, et al. Accumulation of metabolic risk factors such as overweight, hypertension, dyslipidaemia, and impaired glucose tolerance raises the risk of occurrence and progression of knee osteoarthritis: a 3-year follow-up of the ROAD study. Osteoarthritis Cartilage 2012;20:1217–26.
38. Hellevik AI, Johnsen MB, Langhammer A, Baste V, Furnes O, Storheim K, et al. Metabolic syndrome as a risk factor for total hip or knee replacement due to primary osteoarthritis: a prospective cohort study (the HUNT study and the Norwegian Arthroplasty Register). Clin Epidemiol 2018;10:83–96.
39. Shirinsky IV, Shirinsky VS. Effects of medication-treated diabetes on incidence and progression of knee osteoarthritis: a longitudinal analysis of the Osteoarthritis Initiative data. Rheumatol Int 2017;37:983–91.
40. Barnett LA, Jordan KP, Edwards JJ, van der Windt DA. Does metformin protect against osteoarthritis? An electronic health record cohort study. Prim Health Care Res Dev 2017;1–6.
41. Lu CH, Chung CH, Lee CH, Hsieh CH, Hung YJ, Lin FH, et al. Combination COX-2 inhibitor and metformin attenuate rate of joint replacement in osteoarthritis with diabetes: A nationwide, retrospective, matched-cohort study in Taiwan. PLoS One 2018;13:e0191242.

42. Dell'Isola A, Allan R, Smith SL, Marreiros SS, Steultjens M. Identification of clinical phenotypes in knee osteoarthritis: a systematic review of the literature. BMC Musculoskelet Disord 2016;17: 425.
43. Altman R, Asch E, Bloch D, Bole G, Borenstein D, Brandt K, et al. Development of criteria for the classification and reporting of osteoarthritis: classification of osteoarthritis of the knee. Arthritis Rheum 1986;29:1039–49.
44. Horn CA, Bradley JD, Brandt KD, Kreipke DL, Slowman SD, Kalasinski LA. Impairment of osteophyte formation in hyperglycemic patients with type II diabetes mellitus and knee osteoarthritis. Arthritis Rheum 1992;35:336–42.

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Step Rate and Worsening of Patellofemoral and Tibiofemoral Joint Osteoarthritis in Women and Men: The Multicenter Osteoarthritis Study

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Objective. To determine the association of self-selected walking step rate with worsening of cartilage damage in the patellofemoral (PF) joint and tibiofemoral (TF) joint compartments at a 2-year follow-up visit.

Methods. The Multicenter Osteoarthritis Study (MOST) is a prospective cohort of men and women with or at risk of knee osteoarthritis. Self-selected step rate was measured using an instrumented GAITRite walkway (CIR Systems) at the 60-month visit. Cartilage damage was semiquantitatively graded on magnetic resonance images at the 60- and 84-month visits in the medial and lateral PF and TF compartments. Step rate was divided into quartiles, and logistic regression was used to determine the association of step rate with the risk of worsening cartilage damage in men and women separately. Analyses were adjusted for age, body mass index, and knee injury/surgery.

Results. A total of 1,089 participants were included. Mean ± SD age was 66.9 ± 7.5 years, mean ± SD body mass index was 29.6 ± 4.7 kg/m^2, and 62.3% of the participants were women. Women with the lowest step rate had increased risk of lateral PF (risk ratio [RR] 2.1 [95% confidence interval (95% CI) 1.1–3.8]) and TF (RR 1.8 [95% CI 1.1–2.9]) cartilage damage worsening 2 years later compared to those with the highest step rate. Men with the lowest step rate had increased risk of medial TF cartilage damage worsening 2 years later (RR 2.1 [95% CI 1.1–3.9]).

Conclusion. Lower step rate was associated with increased risk of cartilage damage worsening in the lateral PF and TF compartments in women and worsening medial TF joint damage in men. Future research is necessary to understand the influence of step rate manipulation on joint biomechanics in women and men.

INTRODUCTION

Knee osteoarthritis (OA) is estimated to affect 250 million people worldwide and is associated with considerable pain, functional limitations, reduced physical activity levels (1), and diminished overall quality of life (2,3). It can occur in the patellofemoral (PF) joint, the tibiofemoral (TF) joint, or both.

Step rate (i.e., cadence) indicates the number of steps taken per minute. At a fixed walking velocity (distance travelled per minute), step rate is inversely related to step length (distance travelled per step). For example, shortened steps require a greater step rate in order to maintain a constant walking speed. Step rate can influence joint-specific loads and biomechanics. In healthy runners, reduced step rate is associated with greater knee flexion angle, greater peak internal knee extensor moment (4), and increased peak PF load (5). Results of previous studies exploring the influence of step rate manipulation have shown that increasing running step rate while maintaining a constant

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SIGNIFICANCE & INNOVATIONS

- This is the first study to evaluate the association of walking step rate with worsening of cartilage damage in the patellofemoral and tibiofemoral compartments.
- Lower step rate is associated with increased risk of worsening cartilage damage in the lateral patellofemoral and tibiofemoral compartments in women.
- Lower step rate is associated with increased risk of worsening cartilage damage in the medial tibiofemoral compartment in men.
- This knowledge may inform efforts to slow cartilage damage worsening and reduce symptoms; however, further research is required.

speed can reduce loading to the knee joint compartments (4), including reduced TF contact forces (6) and reduced peak PF forces (5) in healthy individuals. Additionally, increasing running step rate can also reduce PF stress and PF reaction forces in individuals with PF pain (7). Based on this, it is possible that step rate may play a role in the development and worsening of OA of the PF and TF joints.

Evidence from a systematic review indicates that individuals with knee OA tend to walk with a reduced step rate (8). However, it is not known whether reduced step rate is an antecedent cause or a subsequent consequence of more severe disease. To our knowledge, there are no longitudinal studies that have investigated the relation of step rate with subsequent worsening of knee OA. Considering the burden of knee OA and ease with which step rate can be assessed and potentially manipulated in the clinic (e.g., smartphone applications, metronomes), it is important to understand the potential influence that self-selected step rate during walking has on subsequent risk of knee OA worsening.

Magnetic resonance imaging (MRI) is more appropriate than radiography to detect the subtle features of OA (9). One must also consider sex-specific differences in step rate (10), compartment-specific prevalence of knee OA (11), and lower extremity biomechanics (12). With these considerations in mind, the current study investigated the relation of self-selected walking step rate to the 2-year risk of worsening MRI-defined cartilage damage in the medial and lateral PF and TF joints among women and men separately within a cohort of individuals that have or are at risk of knee OA.

SUBJECTS AND METHODS

Study population. The Multicenter Osteoarthritis Study (MOST) is an NIH-funded longitudinal, prospective, observational study of 3,026 older adults, ages 50–79 years when enrolled, who have or are at risk of knee OA. Subjects were recruited from Birmingham, Alabama and Iowa City, Iowa. Full details of the study population have been published previously (13). In the current study, a sample of 1,089 individuals who had their step rate assessed at the 60-month clinic visit (the current study's baseline) and had MRI-defined cartilage damage in the PF and TF joints that was assessed at 60 and 84 months as part of the parent MOST study were eligible.

Participant characteristics. Age and body mass index data from the 60-month study visit were included in the current study. A prior history of knee injury or surgery was assessed with 2 questions: "Have you injured your knee badly enough that it limited your ability to walk for at least two days" and "Have you had any surgery in your knee?" Frequent knee pain was assessed in each knee by asking participants, "Do you have knee pain, aching, or stiffness on most days of the month?"

Gait variables. To be eligible for the walking examination at the 60-month follow-up visit, participants had to be able to walk independently over short indoor distances without an assistive device or knee brace. Participants with recent lower-extremity injury (<6 weeks) resulting in restricted weight bearing for ≥1 week, recent hospitalization for a cardiovascular or respiratory disorder, lower-extremity amputation proximal to the toes, or difficulty walking because of a neurologic condition were excluded. Following a practice trial, each participant completed 4 walking trials over a 4.9-meter instrumented GAITRite (CIR Systems) walkway at a self-selected speed. Participants wore their customary walking shoes and were instructed to walk in their usual way, at a pace that felt comfortable and unhurried. To exclude the initial acceleratory and terminal decelerating steps, participants began walking from a point 1.5 meters in front of the walkway and stopped at a point 1.5 meters beyond the walkway. Footfalls were counted between the initial and terminal contacts with the pressure-sensitive walkway. This count was divided by the elapsed time in seconds between these 2 events to obtain the step rate for each trial. Gait speed and step length were simultaneously recorded for each trial. All measured gait parameters were averaged over 4 trials.

MRI acquisition. Knee MRIs were acquired using a 1.0 Tesla extremity MRI unit (OrthOne, GE HealthCare) with a phased-array knee coil to obtain the following sequences: fat-suppressed fast spin-echo proton density–weighted sequences in 2 planes, sagittal (repetition time [TR] 4,800 msec, echo time [TE] 35 msec, 3-mm slice thickness, 0-mm interslice gap, 32 slices, 288 × 192 matrix, 140 mm^2 field of view [FOV], echo train length 8) and axial (TR 4,680 msec, TE 13 msec, 3-mm slice thickness, 0-mm interslice gap, 20 slices, 288 × 192 matrix, 140 mm^2 FOV, echo train length 8) and a STIR sequence in the coronal plane (TR 6,650 msec, TE 15 msec, inversion time 100 msec, 3-mm slice thickness, 0-mm interslice gap, 28 slices, 256 × 192 matrix, 140 mm^2 FOV, echo train length 8).

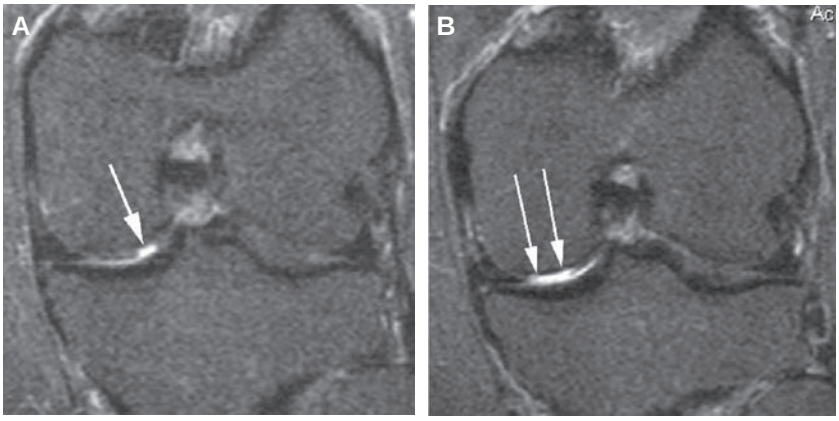

Figure 1. Worsening of focal defect during 24 months of follow-up. **A**, Baseline coronal STIR image shows a full thickness focal defect (Whole-Organ Magnetic Imaging Score grade 2.5) in the central, weight-bearing region of the medial femur (**arrow**); **B**, 24-month follow-up image shows a definite increase in lesion size indicating progression medially (**arrows**).

Patellofemoral and tibiofemoral joint cartilage damage assessment. Two musculoskeletal radiologists (AG and FR) used the Whole-Organ Magnetic Resonance Imaging Score (WORMS) to assess cartilage morphology in the PF and TF joints (14). Four PF and 10 TF subregions per knee were assessed. The PF joint included the medial and lateral patella and medial and lateral trochlea. The TF joint included the medial and lateral tibial plateaus (central, anterior, and posterior subregions) and opposing central and posterior subregions of the femur. Worsening of cartilage damage in each subregion was defined as any increase in WORMS score (≥ 1) from 60 to 84 months in the specific subregion (Figure 1). To increase sensitivity to detect change, within-grade WORMS score changes were also considered indicative of worsening cartilage damage (15). A change from grade 0 to 1 was not considered to be worsening of cartilage damage because grade 1 does not represent a morphologic abnormality. Subregions with a maximal score at 60 months were not eligible for analysis. Inter-reader reliability (weighted kappa) for cartilage damage was 0.85.

Statistical analyses. Step rate was divided into 4 quartiles, and logistic regression analyses were used to determine the association of self-selected walking step rate with worsening of cartilage damage in the PF and TF compartments from 60 (baseline) to 84 months (follow-up). Quartile 4, consisting of knees with the highest step rate, served as the reference group. Since there are sex-specific differences in the compartment-specific prevalence of knee OA (11) and lower extremity biomechanics (12), we carried out sex-specific and compartment-specific analyses. The medial PF (2 subregions), lateral PF (2 subregions), medial TF (5 subregions), and lateral TF (5 subregions) were assessed using 4 separate models (outcomes). Each knee contributed 4 subregions for the PF outcomes (e.g., medial and lateral patella and trochlea) and 10 subregions for TF outcomes (medial and lateral tibia and femur). Generalized estimating equations were used to account for the correlation between subregions within a knee. All analyses were adjusted for age, body mass index, and previous history of knee injury/surgery (yes or no). In an attempt to determine the independent relation of step rate on outcomes, we also created 2 additional models: a main analysis with additional adjustment for step length, and a main analysis with additional adjustment for gait speed. We did not simultaneously adjust for both gait speed and step length because these variables were highly correlated (r = 0.8). Since the presence of knee pain and greater knee OA severity could influence step rate, we further adjusted for the presence of frequent knee pain in either knee and radiographic disease severity at baseline in sensitivity analyses.

RESULTS

The step rate of 678 women and 411 men was assessed at the 60-month study visit as well as MRI-assessed cartilage damage at the 60- and 84-month visits. At the 60-month study visit, the mean ± SD age of the 1,089 participants was 66.9 ± 7.5 years, and the mean ± SD body mass index was 29.6 ± 4.7 kg/m^2 (Table 1).

Relative to women with the highest step rate at baseline, those with the lowest step rate had significantly greater risk of cartilage damage worsening in the lateral PF and TF 2 years

Table 1. Participant characteristics*

	Women (n = 678)	Men (n = 411)
Age, years	67.2 ± 7.4	66.5 ± 7.7
Body mass index, kg/m^2	29.2 ± 4.9	30.1 ± 4.5
Knee injury/surgery, %	26.8	34.6
Step rate, steps/minute	110.8 ± 8.9	104.8 ± 7.6
Gait speed, meters/second	1.16 ± 0.18	1.22 ± 0.18
Knee pain, %	27†	20

* Values are mean ± SD unless indicated otherwise.
† Missing data (n = 1).

Table 2. Relationship of step rate (steps/minute) to worsening cartilage damage in patellofemoral and tibiofemoral joint subregions from 60–84 months in women (n = 678 knees)*

		Worsening lateral cartilage damage		Worsening medial cartilage damage	
	Gait speed, mean ± SD†	Frequency of outcome‡	Adjusted RR (95% CI)§	Frequency of outcome‡	Adjusted RR (95% CI)§
Patellofemoral joint					
Quartile 1 (79.0–105.0)	0.99 ± 0.14	30/304 (9.9)	2.1 (1.1–3.8)	30/326 (9.2)	1.6 (0.9–2.8)
Quartile 2 (105.1–110.7)	1.12 ± 0.12	31/313 (9.9)	2.1 (1.1–3.8)	23/323 (7.1)	1.2 (0.7–2.2)
Quartile 3 (110.8–116.4)	1.22 ± 0.13	29/322 (9.0)	1.9 (1.0–3.5)	25/331 (7.6)	132 (0.7–2.3)
Quartile 4 (116.5–154.4)	1.33 ± 0.15	15/317 (4.7)	1.0 (reference)	19/327 (5.8)	1.0 (reference)
P for linear trend			0.05		0.1
Tibiofemoral joint					
Quartile 1 (79.0–105.0)	0.99 ± 0.14	76/846 (9.0)	1.8 (1.1–2.9)	66/840 (7.9)	1.2 (0.7–1.9)
Quartile 2 (105.1–110.7)	1.12 ± 0.12	66/834 (7.9)	1.6 (1.0–2.5)	72/820 (8.8)	1.3 (0.8–2.1)
Quartile 3 (110.8–116.4)	1.22 ± 0.13	39/844 (4.6)	0.9 (0.5–1.6)	64/837 (7.7)	1.2 (0.7–1.9)
Quartile 4 (116.5–154.4)	1.33 ± 0.15	42/850 (4.9)	1.0 (reference)	53/832 (6.4)	1.0 (reference)
P for linear trend			0.02		0.4

* Values are step rate quartiles (range) unless indicated otherwise. RR = risk ratio; 95% CI = 95% confidence interval.
† Gait speed units = meters/second.
‡ Denominators may vary due to subregions that are unreadable on magnetic resonance imaging or have maximal scores at 60 months.
§ Adjusted for age, body mass index, and previous injury/surgery.

later (Table 2). Specifically, women with the lowest step rate had 2.1 (95% confidence interval [95% CI] 1.1–3.8) and 1.8 (95% CI 1.1–2.9) times the risk of worsening cartilage damage in the lateral PF and TF compartments, respectively. There were no significant associations observed between step rate and worsening of medial PF or TF cartilage damage (Table 2). Results were similar when adjusting for gait speed (Table 3) and step length (see Supplementary Table 1, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23864/abstract) and when adjusting for baseline knee pain and radiographic disease severity during sensitivity analyses (data not presented).

In men, there were no associations between step rate at baseline and worsening of lateral and medial PF cartilage damage 2 years later (Table 4). Similarly, there were no associations between baseline step rate and lateral TF cartilage damage worsening in men. However, compared to those with the highest step rate, men with lowest step rates had ~2 times the risk of medial TF cartilage damage worsening (Table 4). Results were similar when adjusting for gait speed (Table 5) and step length (see Supplemen-

Table 3. Relationship of step rate (steps/minute) to worsening cartilage damage in patellofemoral and tibiofemoral joint subregions from 60–84 months in women (n = 678 knees), adjusted for gait speed*

		Worsening lateral cartilage damage		Worsening medial cartilage damage	
	Gait speed, mean ± SD†	Frequency of outcome‡	Adjusted RR (95% CI)§	Frequency of outcome‡	Adjusted RR (95% CI)§
Patellofemoral joint					
Quartile 1 (79.0–105.0)	0.99 ± 0.14	30/304 (9.9)	2.3 (1.0–5.3)	30/326 (9.2)	1.4 (0.7–2.8)
Quartile 2 (105.1–110.7)	1.12 ± 0.12	31/313 (9.9)	2.2 (1.1–4.6)	23/323 (7.1)	1.1 (0.6–2.1)
Quartile 3 (110.8–116.4)	1.22 ± 0.13	29/322 (9.0)	1.9 (1.0–3.7)	25/331 (7.6)	1.2 (0.7–2.2)
Quartile 4 (116.5–154.4)	1.33 ± 0.15	15/317 (4.7)	1.0 (reference)	19/327 (5.8)	1.0 (reference)
P for linear trend			0.2		0.4
Tibiofemoral joint					
Quartile 1 (79.0–105.0)	0.99 ± 0.14	76/846 (9.0)	2.3 (1.1–4.5)	66/840 (7.9)	1.3 (0.6–2.6)
Quartile 2 (105.1–110.7)	1.12 ± 0.12	66/834 (7.9)	1.8 (1.0–3.3)	72/820 (8.8)	1.4 (0.8–2.5)
Quartile 3 (110.8–116.4)	1.22 ± 0.13	39/844 (4.6)	1.0 (0.6–1.8)	64/837 (7.7)	1.2 (0.7–2.1)
Quartile 4 (116.5–154.4)	1.33 ± 0.15	42/850 (4.9)	1.0 (reference)	53/832 (6.4)	1.0 (reference)
P for linear trend			0.04		0.3

* Values are step rate quartiles (range) unless indicated otherwise. RR = risk ratio; 95% CI = 95% confidence interval.
† Gait speed units = meters/second.
‡ Denominators may vary due to subregions that are unreadable on magnetic resonance imaging or have maximal scores at 60 months.
§ Adjusted for age, body mass index, gait speed, and previous injury/surgery.

Table 4. Relationship of step rate (steps/minute) to worsening cartilage damage in patellofemoral and tibiofemoral joint subregions from 60–84 months in men (n = 411 knees)*

		Worsening lateral cartilage damage		Worsening medial cartilage damage	
	Gait speed, mean ± SD†	Frequency of outcome‡	Adjusted RR (95% CI)§	Frequency of outcome‡	Adjusted RR (95% CI)§
Patellofemoral joint					
Quartile 1 (84.5–100.3)	1.07 ± 0.13	10/192 (5.2)	0.9 (0.4–2.1)	9/196 (4.6)	0.7 (0.3–1.6)
Quartile 2 (100.4–104.5)	1.17 ± 0.13	20/189 (10.6)	1.8 (0.8–3.8)	16/196 (8.2)	1.3 (0.6–2.7)
Quartile 3 (104.6–109.9)	1.27 ± 0.15	20/191 (10.5)	1.8 (0.9–3.8)	14/192 (7.3)	1.0 (0.5–2.3)
Quartile 4 (110.0–128.7)	1.37 ± 0.17	11/193 (5.7)	1.0 (reference)	13/191 (6.8)	1.0 (reference)
P for linear trend			0.7		0.08
Tibiofemoral joint					
Quartile 1 (84.5–100.3)	1.07 ± 0.13	22/518 (4.3)	0.9 (0.4–2.1)	46/514 (9.0)	2.1 (1.1–3.9)
Quartile 2 (100.4–104.5)	1.17 ± 0.13	26/497 (5.2)	1.1 (0.5–2.4)	55/489 (11.3)	2.4 (1.3–4.5)
Quartile 3 (104.6–109.9)	1.27 ± 0.15	18/515 (3.5)	0.8 (0.3–1.8)	31/511 (6.1)	1.5 (0.8–2.8)
Quartile 4 (110.0–128.7)	1.37 ± 0.17	23/515 (4.5)	1.0 (reference)	22/506 (4.4)	1.0 (reference)
P for linear trend			0.9		0.004

* Values are step rate quartiles (range) unless indicated otherwise. RR = risk ratio; 95% CI = 95% confidence interval.
† Gait speed units = meters/second.
‡ Denominators may vary due to subregions that are unreadable on magnetic resonance imaging or have maximal scores at 60 months.
§ Adjusted for age, body mass index, and previous injury/surgery.

tary Table 2, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23864/abstract) and when adjusting for baseline knee pain and radiographic disease severity during sensitivity analyses (data not presented).

DISCUSSION

To our knowledge, the current study is the first to report the association of self-selected step rate with worsening of MRI-defined compartment-specific PF and TF cartilage damage in men and women. Lower step rate was associated with increased risk of cartilage damage worsening 2 years after baseline in the lateral PF and TF compartments in women and in the medial TF compartment in men. These findings highlight a potentially modifiable gait parameter linked to OA worsening in women and men that could be considered in future research and clinical practice.

We observed an association between lower step rate during walking and worsening of cartilage damage 2 years later. The potential mechanism leading to cartilage damage worsening in those who walk with a lower step rate is likely related to adverse loading at the knee joint. However, given that there are no studies that have investigated the influence of step rate manipulation on

Table 5. Relationship of step rate (steps/minute) to worsening cartilage damage in patellofemoral and tibiofemoral joint subregions from 60–84 months in men (n = 411 knees), adjusted for gait speed*

		Worsening lateral cartilage damage		Worsening medial cartilage damage	
	Gait speed, mean ± SD†	Frequency of outcome‡	Adjusted RR (95% CI)§	Frequency of outcome‡	Adjusted RR (95% CI)§
Patellofemoral joint					
Quartile 1 (84.5–100.3)	1.07 ± 0.13	10/192 (5.2)	0.9 (0.3–2.6)	9/196 (4.6)	0.5 (0.2–1.6)
Quartile 2 (100.4–104.5)	1.17 ± 0.13	20/189 (10.6)	1.7 (0.7–4.2)	16/196 (8.2)	1.1 (0.4–2.5)
Quartile 3 (104.6–109.9)	1.27 ± 0.15	20/191 (10.5)	1.8 (0.8–4.0)	14/192 (7.3)	0.9 (0.4–2.1)
Quartile 4 (110.0–128.7)	1.37 ± 0.17	11/193 (5.7)	1.0 (reference)	13/191 (6.8)	1.0 (reference)
P for linear trend			0.6		0.02
Tibiofemoral joint					
Quartile 1 (84.5–100.3)	1.07 ± 0.13	22/518 (4.3)	1.1 (0.4–2.8)	46/514 (9.0)	2.0 (0.9–4.4)
Quartile 2 (100.4–104.5)	1.17 ± 0.13	26/497 (5.2)	1.2 (0.5–3.1)	55/489 (11.3)	2.3 (1.2–4.7)
Quartile 3 (104.6–109.9)	1.27 ± 0.15	18/515 (3.5)	0.8 (0.3–1.9)	31/511 (6.1)	1.4 (0.7–2.9)
Quartile 4 (110.0–128.7)	1.37 ± 0.17	23/515 (4.5)	1.0 (reference)	22/506 (4.4)	1.0 (reference)
P for linear trend			0.9		0.05

* Values are step rate quartiles (range) unless indicated otherwise. RR = risk ratio; 95% CI = 95% confidence interval.
† Gait speed units = meters/second.
‡ Denominators may vary due to subregions that are unreadable on magnetic resonance imaging or have maximal scores at 60 months.
§ Adjusted for age, body mass index, gait speed, and previous injury/surgery.

knee-specific loads during walking, we needed to draw from the literature on step rate manipulation during running for a plausible explanation of the results. It has been reported that decreasing preferred step rate by 10% results in significantly greater peak knee flexion angles and extensor internal moments (4). It also has been reported to result in greater peak PF force and patellar tendon force during running when compared to preferred step rate (5). In addition, lower running step rate is associated with greater peak vastus lateralis force and smaller peak rectus femoris, biceps femoris, and semimembranosus forces compared to the preferred step rate (5). Based on this, a plausible explanation for our findings could be that lower step rate increases peak internal extensor moment, which in turn increases quadriceps muscle force. This additional force being produced by the quadriceps muscle increases joint stress, which in turn may accelerate cartilage damage.

To maintain a given gait speed, a decrease in step rate necessitates a proportional increase in step length. Heiderscheit et al (4) investigated the influence of step rate on biomechanics for running at a constant speed. The authors reported that a 10% decrease in preferred step rate (necessitating a proportional increase in step length) increased knee flexion angle and internal extensor moment. Conversely, increasing step rate (i.e., reducing step length) reduced knee flexion angle and internal extensor moment. Changes in joint mechanics can increase joint reaction forces and/or reduce PF contact area and subsequently can elevate joint stress, which could adversely affect the cartilage (16). Bonacci et al (7) reported that increasing step rate during running reduced peak knee flexion angle and extensor moment and reduced peak PF reaction force and stress in individuals with PF pain. However, it is not known whether step rate manipulation produces similar alterations during walking. Therefore, a biomechanical investigation is warranted. This will provide insight into the potential mechanism leading to cartilage damage worsening in those who walk with a lower step rate. It will also provide insight as to whether increasing step rate during walking has the potential for favorable impact on disease progression.

Previous studies confirm that, on average, women walk slower with a higher step rate and shorter step length (81.6 meters/minute = 116.9 steps/minute × 0.70 meters) compared to men, who walk faster with a longer step length and lower step rate (87.2 meters/minute = 111.4 steps/minute × 0.78 meters) (10). This is consistent with our own observations in women (69.6 meters/minute = 111 steps/minute × 0.62 meters) and men (73.2 meters/minute = 105 steps/minute × 0.69 meters). We observed that lower step rate was associated with worsening of lateral PF and TF cartilage damage in women and medial TF cartilage damage in men. The sex-specific differences in gait patterns (e.g., women walk with greater knee abduction [12]) may contribute a sex-specific difference in the prevalence and worsening of knee OA. Knee alignment may be an intermediate variable on the causal pathway. Varus and valgus malalignment is associated with the progression of medial and lateral TF OA, respectively (17). It is plausible that the lower step rate in women creates greater peak loading on the lateral compartment due to a greater valgus alignment. However, research is necessary to elucidate the influence of preferred step rate on gait patterns in women and men as well as the effects of changing step rate on gait patterns in women and men.

In specialized laboratory and clinical settings, step rate can be increased without increasing gait speed. However, in external environments, increasing step rate may increase walking speed (10), and fast walking has been shown to be associated with increased knee joint moments (18,19). However, recent work by Ardestani et al (20) shows that increasing walking speed by increasing step rate but not stride length does not significantly increase knee joint moments. Exercise programs have been reported to increase step rate in healthy older women (21) and in patients while walking after total hip replacement (22). Thus, similar exercise interventions and wearable technology may be employed to increase step rate during walking in individuals with knee OA (23). However, controlled laboratory-based studies are first required to determine the influence of manipulating step rate on factors such as gait speed and joint biomechanics.

We encourage readers to consider the following limitations when interpreting the results of the current study. First, we investigated the influence of step rate on worsening of cartilage damage. Step rate, step length, and gait speed are interdependent (gait speed = step rate × step length). However, adjusting for gait speed and step length did not substantially alter these results. This suggests that step rate may have a direct impact on knee loading that is not entirely accounted for by changes in other related gait parameters. Second, step rate was measured at a preferred gait speed, and we observed an unexpectedly weak correlation between step rate and step length ($r = 0.10$). Since step rate and step length data were averaged over 4 trials, this may have influenced the results. Further, step rate is a participant-level measure, while step length can differ between legs, and this may also explain the weak correlation observed between these 2 interdependent variables. Last, step rate varies during different tasks during activities of daily living (24), and in the current study, gait assessment was conducted in a laboratory setting, which may have influenced the results. A better understanding of gait parameters during free-living may improve our understanding of disease progression and aid in the development of gait adaptation strategies.

Our findings indicate that a lower self-selected step rate during walking may elevate the risk of cartilage damage worsening in the lateral PF and TF compartments in women and medial TF compartment in men at a 2-year follow-up visit. Further research is required to understand the influence of step rate manipulation on biomechanics during walking in women and men.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Stefanik had full access to

all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Hart, Crossley, Stefanik.

Acquisition of data. Gross, Felson, Segal, Lewis, Nevitt.

Analysis and interpretation of data. Hart, Gross, Crossley, Barton, Felson, Guermazi, Roemer, Segal, Lewis, Nevitt, Stefanik.

REFERENCES

1. Vos T, Flaxman AD, Naghavi M, Lozano R, Michaud C, Ezzati M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012;380:2163–96.
2. Cross M, Smith E, Hoy D, Nolte S, Ackerman I, Fransen M, et al. The global burden of hip and knee osteoarthritis: estimates from the global burden of disease 2010 study. Ann Rheum Dis 2014;73:1323–30.
3. Farr IJ, Miller LE, Block JE. Quality of life in patients with knee osteoarthritis: a commentary on nonsurgical and surgical treatments. Open Orthop J 2013;7:619–23.
4. Heiderscheit BC, Chumanov ES, Michalski MP, Wille CM, Ryan MB. Effects of step rate manipulation on joint mechanics during running. Med Sci Sports Exerc 2011;43:296–302.
5. Lenhart RL, Thelen DG, Wille CM, Chumanov ES, Heiderscheit BC. Increasing running step rate reduces patellofemoral joint forces. Med Sci Sports Exerc 2014;46:557–64.
6. Willy RW, Meardon SA, Schmidt A, Blaylock NR, Hadding SA, Willson JD. Changes in tibiofemoral contact forces during running in response to in-field gait retraining. J Sports Sci 2016;34:1602–11.
7. Bonacci J, Hall M, Fox A, Saunders N, Shipsides T, Vicenzino B. The influence of cadence and shoes on patellofemoral joint kinetics in runners with patellofemoral pain. J Sci Med Sport 2018;21:574–8.
8. Mills K, Hunt MA, Ferber R. Biomechanical deviations during level walking associated with knee osteoarthritis: a systematic review and meta-analysis. Arthritis Care Res (Hoboken) 2013;65:1643–65.
9. Guermazi A, Hayashi D, Roemer F, Felson DT, Wang K, Lynch J, et al. Severe radiographic knee osteoarthritis: does Kellgren and Lawrence grade 4 represent end stage disease? The MOST study. Osteoarthritis Cartilage 2015;23:1499–505.
10. Zatsiorky VM, Werner SL, Kaimin MA. Basic kinematics of walking: step length and step frequency. A review. J Sports Med Phys Fitness 1994;34:109–34.
11. McAlindon TE, Snow S, Cooper C, Dieppe PA. Radiographic patterns of osteoarthritis of the knee joint in the community: the importance of the patellofemoral joint. Ann Rheum Dis 1992;51:844–9.
12. Phinyomark A, Osis ST, Hettinga BA, Kobsar D, Ferber R. Gender differences in gait kinematics for patients with knee osteoarthritis. BMC Musculoskelet Disord 2016;17:157.
13. Segal NA, Nevitt MC, Gross KD, Hietpas J, Glass NA, Lewis CE, et al. The Multicenter Osteoarthritis Study: opportunities for rehabilitation research. PM R 2013;5:647–54.
14. Peterfy CG, Guermazi A, Zaim S, Tirman PF, Miaux Y, White D, et al. Whole-Organ Magnetic Resonance Imaging Score (WORMS) of the knee in osteoarthritis. Osteoarthritis Cartilage 2004;12:177–90.
15. Roemer FW, Nevitt MC, Felson DT, Niu J, Lynch JA, Crema MD, et al. Predictive validity of within-grade scoring of longitudinal changes of MRI-based cartilage morphology and bone marrow lesion assessment in the tibio-femoral joint: the MOST study. Osteoarthritis Cartilage 2012;20:1391–8.
16. Fulkerson JP, Shea KP. Mechanical basis for patellofemoral pain and cartilage breakdown. In: Ewing JW, editor. Articular cartilage and knee joint function: basic science and arthroscopy. New York: Raven Press; 1990.
17. Sharma L, Song J, Dunlop D, Felson D, Lewis CE, Segal N, et al. Varus and valgus alignment and incident and progressive knee osteoarthritis. Ann Rheum Dis 2010;69:1940–5.
18. Watt JR, Franz JR, Jackson K, Dicharry J, Riley PO, Kerrigan DC. A three-dimensional kinematic and kinetic comparison of overground and treadmill walking in healthy elderly subjects. Clin Biomech (Bristol, Avon) 2010;25:444–9.
19. Lelas JL, Merriman GJ, Riley PO, Kerrigan DC. Predicting peak kinematic and kinetic parameters from gait speed. Gait Posture 2003;17:106–12.
20. Ardestani MM, Ferrigno C, Moazen M, Wimmer MA. From normal to fast walking: impact of cadence and stride length on lower extremity joint moments. Gait Posture 2016;46:118–25.
21. Lord SR, Lloyd DG, Nirui M, Raymond J, Williams P, Stewart RA. The effect of exercise on gait patterns in older women: a randomized controlled trial. J Gerontol A Biol Sci Med Sci 1996;51:M64–70.
22. Coulter CL, Scarvell JM, Neeman TM, Smith PN. Physiotherapist-directed rehabilitation exercises in the outpatient or home setting improve strength, gait speed and cadence after elective total hip replacement: a systematic review. J Physiother 2013;59:219–26.
23. Willy RW, Buchenic L, Rogacki K, Ackerman J, Schmidt A, Willson JD. In-field gait retraining and mobile monitoring to address running biomechanics associated with tibial stress fracture. Scand J Med Sci Sports 2016;26:197–205.
24. Tudor-Locke C, Rowe DA. Using cadence to study free-living ambulatory behaviour. Sports Med 2012;42:381–98.

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Association of Pain and Steps Per Day in Persons With Mild-to-Moderate, Symptomatic Knee Osteoarthritis: A Mixed-Effects Models Analysis of Multiple Measurements Over Three Years

Nicholas M. Brisson,[1] Anthony A. Gatti,[2] and Monica R. Maly[3]

Objective. Pain is a consistently reported barrier to physical activity by persons with knee osteoarthritis (OA). Nonetheless, few studies of knee OA have investigated the association of pain with daily walking levels. The current study assessed the relationship of 2 distinct measures of knee pain with objectively measured physical activity in adults with knee OA.

Methods. This was a longitudinal, observational investigation of 59 individuals (48 women; mean ± SD age 61.1 ± 6.4 years, mean ± SD body mass index 28.1 ± 5.6 kg/m^2) with clinical knee OA. Data were collected every 3 months for up to 3 years. Physical activity was characterized as the average steps per day taken over at least 3 days, measured by accelerometry. Pain was measured using 2 patient-administered questionnaires: the pain subscale of the Knee Injury and Osteoarthritis Outcome Score (KOOS-pain) and the P4 pain scale (P4-pain). Mixed-effects models determined the association between pain and physical activity levels (over covariates) among adults with knee OA ($\alpha = 0.05$).

Results. All covariates (age [$\beta = -3.65$, $P < 0.001$], body mass index [$\beta = -3.06$, $P < 0.001$], season [spring/fall $\beta = -6.91$, $P = 0.002$; winter $\beta = -14.92$, $P < 0.001$]) were predictors of physical activity. Neither the inverted KOOS-pain ($\beta = 0.04$, $P = 0.717$) nor P4-pain ($\beta = -0.37$, $P = 0.264$) was associated with physical activity.

Conclusion. Knee pain is not associated with daily walking levels in persons with mild-to-moderate, symptomatic knee OA. While pain management remains an important target of interventions, strategies to increase steps per day in this population should focus on overcoming potentially more crucial barriers to activity participation.

INTRODUCTION

Knee osteoarthritis (OA) is the leading cause of pain, restricted mobility, and disability in older adults (1). Physical activity is recommended for the management of knee OA because it can effectively improve symptoms, including joint pain, as well as physical function and quality of life (2,3). Despite the benefits of physical activity, persons with knee OA engage in less physical activity compared to their healthy counterparts (4–6) and fail to achieve recommended public health guidelines (7,8). Physical activity participation in this clinical population is influenced by numerous factors (e.g., personal, social, bodily, situational, and environmental) (9,10). Of particular interest is disease-related pain, which is one of the most consistently cited barriers to physical activity in knee OA (9,10).

The question of whether pain is associated with physical activity in knee OA has been the focus of ample work, including systematic reviews (11,12). Nonetheless, the link between pain and physical activity remains ambiguous (11–13). Inconsistencies in study findings are likely attributable to the heterogeneity in the methods used to measure physical activity. To reduce self-report biases, the use of objective measures such as accelerometry is recommended (14,15).

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SIGNIFICANCE & INNOVATIONS

- Pain is a consistently reported barrier to physical activity in knee osteoarthritis (OA); yet, the link between pain and physical activity remains ambiguous.
- This longitudinal, repeated-measures study examined the relationship between pain measurements and steps per day (measured with accelerometry).
- Mixed-effects models, which allow analysis of multiple correlated measurements per participant over time, were applied.
- Knee pain was not associated with daily walking levels in mild-to-moderate, symptomatic knee OA.

Objectively-measured physical activity has been characterized in various ways, including activity frequency (e.g., steps/day) (5,6,13,16–18) and intensity (e.g., light, moderate, vigorous) (7,8,19). Few knee OA studies have formally investigated the association of pain with physical activity, measured objectively as steps per day (13,17,18). Cross-sectionally, pain intensity during activities of daily living was not correlated with steps per day in 160 sedentary overweight/obese adults (17). Only 1 known longitudinal study has directly assessed the relationship between pain and steps per day (13). No association was found between consistent frequent knee pain at baseline and worsening knee pain over 2 years and change in physical activity over 2 years in 1,318 older community-dwelling adults at risk of or with radiographic evidence of knee OA (13).

In order to gain a better understanding of the relationship between pain and physical activity in knee OA, it is essential to account concurrently for the intraindividual and interindividual relationships between pain and physical activity, which can only be accomplished using repeated measures. Furthermore, few longitudinal studies have explored the associations between pain and physical activity. In order to properly analyze multiple correlated measurements per participant over time and deal with missing values, it is imperative that appropriate analyses, such as mixed-effects models, be applied (20). Ascertaining whether pain that is experienced by persons with knee OA is actually associated with reduced walking levels has important implications for disease management.

The primary purpose of this study was to determine the relationship of 2 distinct measures of knee pain with objectively measured physical activity (i.e., steps/day) in adults with clinical knee OA using data acquired every 3 months for up to 3 years. One instrument captured knee pain levels during specific activities over the week prior to physical activity measurements; the other captured diurnal and general activity-related knee pain levels during days that physical activity was recorded. It was hypothesized that by assessing repeated measurements, pain measured using either instrument would be inversely associated with physical activity. A secondary objective was to explore the relationship between the 2 knee pain measures to ascertain whether these demonstrated convergent construct validity.

PATIENTS AND METHODS

Participants. A convenience sample of consecutive individuals satisfying the eligibility criteria was recruited locally from rheumatology and orthopedic surgery offices. Eligibility criteria included being 40–70 years old and diagnosed with clinical knee OA according to the American College of Rheumatology specifications (21). During recruitment, potential participants were excluded for the following reasons: if they required the use of an adaptive walking aid; if they reported other types of arthritis, a history of lower extremity injury and/or surgery, or ipsilateral hip or ankle conditions; if they had experienced lower extremity trauma or used intraarticular therapies within the previous 3 months; or if they were unable to ascend and descend a 9-step staircase twice consecutively. In cases where participants had bilateral knee OA, the most symptomatic knee was appointed as the study leg. In total, 64 participants met the inclusion/exclusion criteria and were enrolled. All participants provided written, informed consent prior to participating.

Descriptive characteristics of the participants were recorded, including sex, age, height, body mass, and body mass index. Additional data were collected at baseline to characterize clinical and structural disease severities. We used the Knee Injury and Osteoarthritis Outcome Score (KOOS) to assess patients' perceptions of their knee OA (22). The Six-Minute Walk Test, a submaximal task that evaluates walking capacity over long distances, was used to describe functional capacity (23,24). In order to characterize radiographic OA severity at baseline, Kellgren/Lawrence scores (25,26) were derived by an experienced radiologist from digital anteroposterior, weight-bearing, knee radiographs acquired in a standardized fixed-flexion position (27).

This longitudinal, observational study was approved by the Hamilton Integrated Research Ethics Board at McMaster University, Canada. Data were collected from this prospective cohort at 3-month intervals over a maximum of 3 years.

Physical activity. Physical activity was measured using a GT3X+ accelerometer (ActiGraph). Participants were instructed to wear the accelerometer, which was fixed to an adjustable belt, around their waist and aligned with the anterolateral aspect of the study leg. Participants were asked to wear the accelerometer for 7 consecutive days during waking hours, except during water activities. Vertical accelerations from body movements were sampled at 30 Hz and accumulated over 60-second epochs to yield step counts (i.e., number of steps taken). Accelerometer wear time and number of steps per day were calculated using ActiLife software, version 6 (ActiGraph). Only days during which the accelerometer was worn for at

least 10 hours were considered valid and retained for further analysis (28). Physical activity was characterized as the average number of total steps per day (from both legs) taken over at least 3 days (and up to 7 days) with complete data (29,30). Accelerometer data captured over 3 days yielded reliable estimates of daily physical activity in older adults (intraclass correlation coefficient [ICC] 0.80) (29).

Pain measures. Pain was measured using 2 patient-administered questionnaires: the pain subscale of the KOOS (KOOS-pain) (22) and the P4 pain scale (P4-pain) (31,32). The KOOS-pain is a disease-specific instrument recommended for the evaluation of pain in knee OA (33,34). The KOOS-pain contains 9, 5-level items about knee pain intensity (n = 8) and frequency (n = 1) during daily activities over the previous week. Each item is rated and converted into scores from 0 (no problem) to 4 (extreme problem). The KOOS-pain was reported as the inverted normalized mean score (of 100), with higher scores indicating more pain (22). Inverted KOOS-pain scores were used to facilitate the interpretation of results by aligning the direction of scores from the KOOS-pain and P4-pain. The KOOS-pain was administered the day before the patient wore the accelerometer, thus reflecting pain levels during the week prior to the physical activity measurements. Data from the KOOS-pain demonstrated the following measurement properties in persons with knee OA: internal consistency (pooled Cronbach's α = 0.84), test–retest reliability (pooled ICC 0.90), and absolute measurement error (standard error of measurement = 9.5) (35).

The P4-pain is a generic pain measure developed for musculoskeletal conditions. The P4-pain includes 4 items about knee pain intensity in the morning, afternoon, evening, and with activity over the previous 2 days. Each item is scored from 0 (no pain) to 10 (pain as bad as it can be) on an 11-point numerical pain rating scale, and the scores of all the items are tallied (of 40), with higher scores indicating more pain (31,32). The P4-pain was recorded on 4 occasions (every 2 days over 8 days) and analyzed as the average of 4 measurements taken concurrently during days that physical activity was recorded. Data from the P4-pain showed the following measurement properties in patients with knee OA: internal consistency (Cronbach's α = 0.91), test-retest reliability (ICC 0.72), and absolute measurement error (standard error of measurement = 4.5) (36).

Statistical analysis. Mixed-effects models were employed because they allow analysis of repeated measurements on the same participants without violating assumptions of independence necessary for linear regression. To answer the primary research question, 3 models were created and compared. Each model included physical activity (i.e., steps/day) as the dependent variable. The first model included only theoretical covariates as predictors of physical activity: age, body mass index (BMI), and meteorologic season. Older age (4,6), higher BMI (4,6), and winter season (37,38) are associated with reduced physical activity levels. Meteorologic seasons were defined as follows: summer (June to August), spring/fall (March to May/September to November), and winter (December to February). Spring and fall were combined because meteorologic conditions during these months are comparable in Canada. The predictor season was dummy-coded using summer as the reference season, thus comparing how physical activity during spring/fall and winter was different from summer. The second and third models were generated by adding the KOOS-pain and the P4-pain, respectively, to the covariate model. Each model was fit using maximum likelihood estimation. The overall predictive ability of the KOOS-pain and P4-pain models was compared to the covariate model using the likelihood ratio test. All tests used a statistical significance threshold set to an alpha level of 0.05. Assumptions, including normality of residuals and homogeneity of variance, were assessed. To satisfy assumptions, all models used log-transformed physical activity as the dependent variable as well as a random intercept grouped by participant. Random intercept and random slope models were assessed; only the random intercept model significantly improved model fit (likelihood ratio test $P < 0.001$) and model assumptions (normality of residuals). All analyses were performed in Stata, version 13.1. To facilitate interpretation of the log-transformed data, the presented β coefficients were transformed ([exp(β) – 1] × 100) and represent the percentage change in the dependent variable for a 1-unit change in the predictor.

To answer the secondary research question, a mixed-effects model was employed. The model included KOOS-pain

Table 1. Descriptive statistics of 59 participants at baseline (48 women)*

Variable	Mean ± SD	Range
Age, years	61.1 ± 6.4	41–69
Height, meters	1.63 ± 0.09	1.46–1.94
Body mass, kg	75.0 ± 16.1	49.4–117.0
Body mass index, kg/m^2	28.1 ± 5.6	19.7–41.8
Other symptoms†	24.5 ± 15.8	0–75
Function in daily living†	18.1 ± 15.4	0–59
Function in sports and recreation, n = 57†	31.0 ± 22.9	0–85
Knee-related quality of life, n = 58†	35.4 ± 18.7	0–87
Six-Minute Walk Test, meters	528.4 ± 99.3	246–771
KOOS-pain†	24.6 ± 17.1	0–62
P4-pain‡	6.4 ± 6.6	0–25
Physical activity, steps/day	7,158 ± 3,071	1,274–20,895

* KOOS-pain = Knee Injury and Osteoarthritis Outcome Score pain subscale; P4-pain = P4 pain scale.
† Measured with subscales of the KOOS (22). Inverted KOOS scores were used. Scores range 0–100, where higher scores reflect worse symptoms and function.
‡ Measured with the P4 pain scale (31). Scores range 0–40, where higher scores reflect more pain.

as the dependent variable and P4-pain as the independent variable. It also utilized a random intercept grouped by participant to achieve assumptions of normality and homoscedasticity. To provide an indicator of convergent construct validity, the coefficient of determination (R^2) for the fixed portions of the fitted model was calculated (R^2 = 1 – [sum of squares$_{residual}$ / sum of squares$_{total}$]).

RESULTS

Data from 59 participants (of 64 participants who enrolled) were included in the current analysis. Only participants with valid/complete data for all 3 measures of interest (i.e., KOOS-pain, P4-pain, physical activity) for at least 2 time points (i.e., repeated-measures) were retained. Data from 5 of the 64 participants who enrolled were excluded entirely from the analysis due to missing data (see Supplementary Figure 1, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23842/abstract). The final sample used for analysis comprised 11 men and 48 women, with the following baseline Kellgren/Lawrence scores: grade I = 2; II = 23; III = 20; IV = 14. Additional baseline descriptive statistics are given in Table 1. All models included 513 observations from 59 participants collected over a maximum of 3 years. The number of observations per participant ranged from 2 to 13, with a mean ± SD 8.7 ± 3.5 observations. In order to demonstrate the intraparticipant and interparticipant variability in outcome measures over the course of the study, average measurements (with 95% confidence intervals for the measurements) for physical activity, KOOS-pain, and P4-pain are plotted for each participant

Table 2. Associations of covariates (age, BMI, season) and potential predictors (KOOS-pain, P4-pain) with the dependent variable (physical activity measured as steps per day)*

Model	Predictor	β coefficient	Variance	*P*
Covariates Log likelihood = –18.88; Wald $\chi^2(4)$ = 95.41; *P* < 0.001				
	Age, years	–3.65		<0.001†
	BMI	–3.06		<0.001†
	Spring/fall	–6.91		0.002†
	Winter	–14.92		<0.001†
	Random intercept		0.154	
	Residual		0.043	
KOOS-pain Log likelihood = –18.81; Wald $\chi^2(5)$ = 95.57; *P* < 0.001				
	Age, years	–3.68		<0.001†
	BMI	–3.10		<0.001†
	Spring/fall	–6.89		0.003†
	Winter	–14.88		<0.001†
	KOOS-pain (22)‡	0.04		0.717
	Random intercept		0.155	
	Residual		0.043	
P4-pain Log likelihood = –18.25; Wald $\chi^2(5)$ = 96.89; *P* < 0.001				
	Age, years	–3.54		<0.001†
	BMI	–2.90		<0.001†
	Spring/fall	–6.93		0.002†
	Winter	–15.16		<0.001†
	P4-pain (31)§	–0.37		0.264
	Random intercept		0.151	
	Residual		0.043	

* All models used log-transformed physical activity as the dependent variable and a random intercept grouped by participant. To facilitate interpretation, β coefficients were transformed ([exp(β) − 1] × 100) and represent the percentage change in the dependent variable for a 1-unit change in the predictor. All models included 59 groups (participants) and 513 observations. Summer was used as the reference season. Seasons were defined as summer (June–August), spring/fall (March–May/September–November), and winter (December–February). BMI = body mass index; KOOS-pain = Knee Injury and Osteoarthritis Outcome Score pain subscale; P4-pain = P4 pain scale.
† Significant (*P* < 0.05).
‡ Inverted KOOS-pain scores were used. Scores range 0–100, where higher scores reflect more pain.
§ Scores range 0–40, where higher scores reflect more pain.

(see Supplementary Figures 2, 3, and 4 at http://onlinelibrary.wiley.com/doi/10.1002/acr.23842/abstract).

Association between pain and physical activity. The covariate model revealed that age (β = –3.65, $P < 0.001$) (see Supplementary Figure 5, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23842/abstract) and BMI (β = –3.06, $P < 0.001$) (see Supplementary Figure 6 at http://onlinelibrary.wiley.com/doi/10.1002/acr.23842/abstract) were inversely related to physical activity (Table 2). The seasons of spring/fall (β = –6.91, $P = 0.002$) and winter (β = –14.92, $P < 0.001$) were associated with lower levels of physical activity compared to summer, with winter having the least activity (see Supplementary Figure 7, at http://onlinelibrary.wiley.com/doi/10.1002/acr.23842/abstract). The second model, which included the inverted KOOS-pain (β = 0.04, $P = 0.717$) (Figure 1), did not differ significantly from the covariate model (likelihood ratio test $\chi^2[1] = 0.13$, $P = 0.718$). The third model, which included P4-pain (β = –0.37, $P = 0.264$) (Figure 2), did not differ significantly from the covariate model (likelihood ratio test $\chi^2[1] = 1.24$, $P = 0.266$).

Association between KOOS-pain and P4-pain. While visualizing scatterplots and residual-versus-fitted plots for a linear fit between KOOS-pain and P4-pain, it was determined that the relationship was nonlinear; thus, a squared term (P4-pain^2) was included. The model investigating the relationship between the 2 pain measures revealed that P4-pain (β = 2.370, $P < 0.001$) and P4-pain^2 (β = –0.042, $P < 0.001$) were significant predictors of the inverted KOOS-pain (Table 3) (Figure 3). The fixed effects of the fitted model yielded an R^2 of 0.579, demonstrating that these measures possessed high convergent validity.

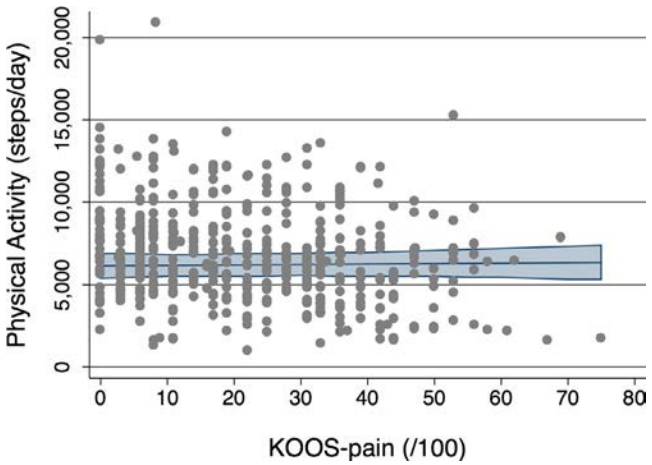

Figure 1. Fitted physical activity (back-transformed) as a function of the Knee Injury and Osteoarthritis Outcome Score (KOOS-pain) and the coinciding 95% confidence interval band. Individual measurements are plotted in gray (n = 513). Physical activity was characterized as the average number of total steps per day (from both legs) taken over at least 3 days (and up to 7 days), measured by an accelerometer. The inverted KOOS-pain scores were reported of 100, with higher scores indicating more pain. KOOS-pain scores reflected knee pain levels during daily activities over the week prior to the physical activity measurements (22).

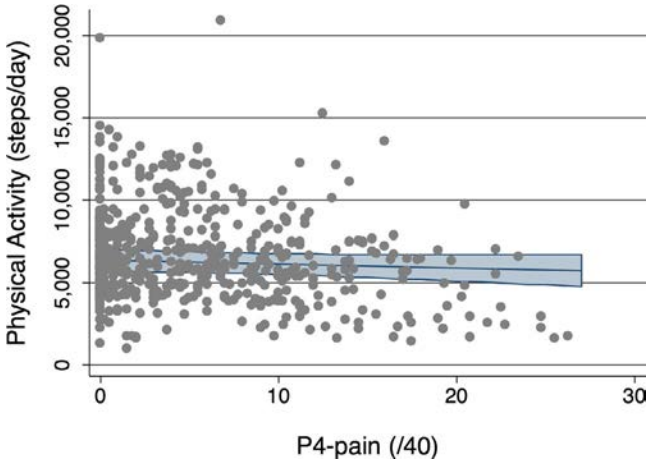

Figure 2. Fitted physical activity (back-transformed) as a function of the P4 pain scale (P4-pain) and the coinciding 95% confidence interval band. Individual measurements are plotted in gray (n = 513). Physical activity was characterized as the average number of total steps per day (from both legs) taken over at least 3 days (and up to 7 days), measured by an accelerometer. P4-pain scores were reported of 40, with higher scores indicating more pain (31). P4-pain scores reflected a 4-measurement average of diurnal and activity-related knee pain levels over 8 days, measured concurrently with physical activity measurements.

DISCUSSION

In the current study, disease-related knee pain was not associated with steps per day in persons with mild-to-moderate, symptomatic knee OA. This study sought to improve our understanding of the complex relationship between pain severity and physical activity habits in knee OA. The novel contribution and primary strength of this study were the use of multiple measurements to account for potential intraindividual and interindividual relationships, which allowed us to ascertain whether within- and between-participant fluctuations in pain are related to physical activity levels. Results suggest that daily walking levels observed in persons with knee OA are not explained by knee pain severity, emphasizing the notion that pain is not a primary barrier to physical activity participation in this population. Therefore, while pain management remains an important target of clinical interventions, pain alleviation is not likely to increase physical activity levels. Strategies aiming to increase steps per day in knee OA should focus on overcoming potentially more crucial barriers to activity participation, such as lack of knowledge and motivation as well as overall sedentary lifestyle.

Some prior evidence supports the absence of a relationship between knee pain and steps per day in persons with knee OA (13,17). Along with the current investigation, these studies utilized

Table 3. Relationship between P4-pain and KOOS-pain measures*

Model	Predictor	β coefficient	Variance	SE	*P*
P4-pain and KOOS-pain Log likelihood = –1,799.44; Wald $\chi^2(2)=237.11$; $P < 0.001$					
	Intercept	11.928		1.429	<0.001†
	P4-pain	2.370		0.011	<0.001†
	P4-pain^2	–0.042		0.011	<0.001†
	Random intercept		65.191	14.846	
	Residual		49.290	3.320	

* A squared term (P4-pain^2) was included to model the nonlinear relationship visualized between measures. The model included 59 groups (participants), 513 observations, and a random intercept grouped by participant. Values are P4-pain (31) and the inverted score from the pain subscale of the KOOS-pain (Knee Injury and Osteoarthritis Outcome Score pain subscale) (22). For both the P4-pain and KOOS-pain, higher scores reflect more pain. P4-pain = P4 pain scale.
† Significant ($P < 0.05$).

objectively measured steps per day as a measure of physical activity, and they measured pain using standardized, validated instruments. In contrast, only 1 known study (cross-sectional) reported an association between daily walking levels and pain (18). It should be noted that this association was only found for specific activities and subgroups, and pain was analyzed using single-item scores rather than the recommended subscale total scores (18). Caution should be taken in interpreting these findings because testing individual items in multiple subgroups inflates the Type I error rate. While it is conceivable that daily walking levels may be associated with activity-specific pain intensity depending on disease severity, such speculations remain to be examined longitudinally using standardized, validated instruments.

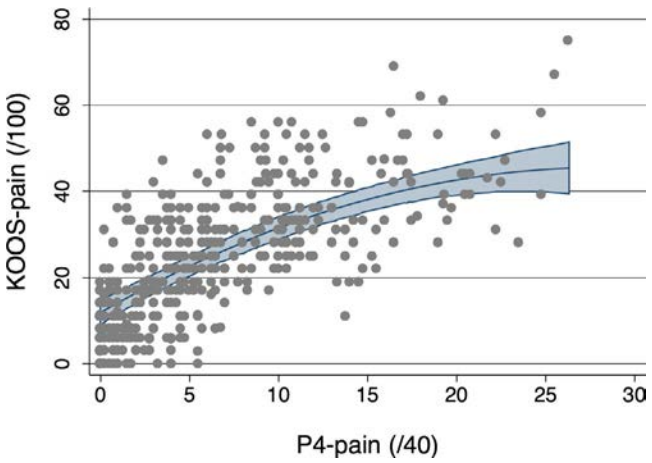

Figure 3. Fitted Knee Injury and Osteoarthritis Outcome Score (KOOS-pain) as a function of the P4 pain scale (P4-pain) and the coinciding 95% confidence interval band. Individual measurements are plotted in gray (n = 513). The inverted KOOS-pain scores were reported of 100, with higher scores indicating more pain. KOOS-pain scores reflected knee pain levels during daily activities over the week prior to the physical activity measurements (22). P4-pain scores were reported of 40, with higher scores indicating more pain (31). P4-pain scores reflected a 4-measurement average of diurnal and activity-related knee pain levels over 8 days, measured concurrently with physical activity measurements. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/acr.23842/abstract.

The current study expands on previous investigations by evaluating pain using 2 distinct, validated and reliable instruments: the 9-item KOOS-pain, which reflected knee pain levels during specific activities over the week prior to physical activity measurements; and the P4-pain scale, which reflected diurnal and general activity-related knee pain levels during days that physical activity was recorded. Considered collectively, findings from the present and past studies provide robust evidence that knee pain severity is not related to steps per day in knee OA. Specifically, findings persisted regardless of the instruments used to assess pain, the interval over which pain was recorded relative to physical activity, and whether pain was captured during activities of daily living, at different times of day, or with general activity. It should be noted, however, that results from the current study were observed in a sample of individuals who exhibited relatively mild disease-related symptoms; mean ± SD pain scores at baseline were 24.6 ± 17.1 (of 100) for the inverted KOOS-pain and 6.4 ± 6.6 (of 40) for P4-pain. Pain scores were not discretely reported in the other longitudinal work (13), while the sample from the cross-sectional study also displayed relatively low pain levels (mean ± SD 5.8 ± 2.8 [of 20] for the Western Ontario and McMaster Universities Osteoarthritis Index pain subscale [WOMAC-pain]) (17). It may be that pain intensity in these investigations was not high enough to have an impact on daily walking levels. Conversely, it may be that these individuals were not active enough for their physical activity habits to be altered significantly due to knee pain.

Despite the many benefits of regular physical activity to the management of knee OA, many persons with this condition fail to achieve recommended levels (7,8). This fact reinforces the notion that physical activity should be at the core of treatment strategies for knee OA. It is critical to identify factors that can hinder daily walking behaviors in at-risk populations. Findings from this study help to advance this goal by confirming that knee pain levels (a factor popularly believed to be a primary cause of reduced physical activity in knee OA) are not associated with intraindividual or interindividual fluctuations in walking levels. Accordingly, strategies aiming to increase physical activity in this patient group must overcome other potential key barriers (9,39,40), possibly by tailoring interventions to individual patient preferences and needs

and by providing access to proven supplemental resources (e.g., patient advice/education, arthritis self-management programs, incentives) (41–43).

A secondary objective of this work was to explore the relationship between the KOOS-pain and the P4-pain measurements in this sample. Results from the mixed effects model demonstrated a slight curvilinear relationship between the 2 measures (R^2 = 0.579), indicating stronger agreement than that reported between the P4-pain and WOMAC-pain (r = 0.67, R^2 = 0.449) (44). Imperfect agreement between the P4-pain and KOOS-pain measures (i.e., $R^2 < 1.0$) is to be expected for several reasons. First, each instrument assessed pain over a different timeframe (i.e., the week preceding and the week corresponding to physical activity measurements). Second, the P4-pain asked about pain at different times of day (i.e., morning, afternoon, evening) and with activity, while the KOOS-pain asked about pain with specific activities of daily living. A strong but imperfect agreement suggests that these measures effectively assess the construct of pain but also that multiple measures should be used when conducting analyses aiming to capture all relevant themes of pain.

Limitations of this study should be acknowledged. The study design precluded the establishment of directionality between change in pain and physical activity. That is, pain may have already altered activity participation, and vice versa, prior to the study. Only pain in the study leg was evaluated; pain in the contralateral leg of participants with bilateral knee OA was not controlled for in the analyses. No insight was gained into the relationship between knee pain and other measures of activity (e.g., intensity, type). In addition, 2 distinct pain measures were used in this study; nonetheless, neither one discriminated between types of pain (i.e., constant, intermittent), and only 1 item about pain frequency (KOOS-pain) was included. Future work should examine the relationship between physical activity and different pain domains. Furthermore, while the mixed-effects models adjusted for important covariates, including age, BMI, and season, they did not control for additional variables that could have potentially influenced physical activity levels, such as self-efficacy (45), depressive symptoms (13), fatigue (46), pain-related activity interference (47), and education status (48). Finally, although the sample in the current study was selected based on clinical knee OA criteria, participants exhibited relatively high function and low levels of pain and other symptoms. Thus, results can only be generalized to persons with matching characteristics.

In conclusion, knee pain severity is not associated with physical activity levels, measured objectively as steps per day, in persons with mild-to-moderate, symptomatic knee OA. Walking levels in individuals with knee OA are likely influenced more strongly by factors other than disease-related pain. Interventions aiming to augment daily walking levels in this clinical population should focus on overcoming key barriers to physical activity participation and adherence while conjointly attending to pain and symptom management.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Maly had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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REFERENCES

1. Litwic A, Edwards MH, Dennison EM, Cooper C. Epidemiology and burden of osteoarthritis. Br Med Bull 2013;105:185–99.
2. Fransen M, Mcconnell S. Exercise for osteoarthritis of the knee [review]. Cochrane Libr 2015;1–94.
3. Quicke JG, Foster NE, Thomas MJ, Holden MA. Is long-term physical activity safe for older adults with knee pain? A systematic review. Osteoarthritis Cartilage 2015;23:1445–56.
4. De Groot IB, Bussmann JB, Stam HJ, Verhaar JA. Actual everyday physical activity in patients with end-stage hip or knee osteoarthritis compared with healthy controls. Osteoarthritis Cartilage 2008;16:436–42.
5. Verlaan L, Bolink SA, Van Laarhoven SN, Lipperts M, Heyligers IC, Grimm B, et al. Accelerometer-based physical activity monitoring in patients with knee osteoarthritis: objective and ambulatory assessment of actual physical activity during daily life circumstances. Open Biomed Eng J 2015;9:157–63.
6. Holsgaard-Larsen A, Roos E. Objectively measured physical activity in patients with end stage knee or hip osteoarthritis. Eur J Phys Rehabil Med 2012;48:577–85.
7. Dunlop DD, Song J, Semanik PA, Chang RW, Sharma L, Bathon JM, et al. Objective physical activity measurement in the Osteoarthritis Initiative: are guidelines being met? Arthritis Rheum 2011;63:3372–82.
8. Farr JN, Going SB, Lohman TG, Rankin L, Kasle S, Cornett M, et al. Physical activity levels in patients with early knee osteoarthritis measured by accelerometry. Arthritis Rheum 2008;59:1229–36.
9. Marks R. Knee osteoarthritis and exercise adherence: a review. Curr Aging Sci 2012;5:72–83.
10. Kanavaki AM, Rushton A, Efstathiou N, Alrushud A, Klocke R, Abhishek A, et al. Barriers and facilitators of physical activity in knee and hip osteoarthritis: a systematic review of qualitative evidence. BMJ Open 2017;7:e017042.
11. Veenhof C, Huisman PA, Barten JA, Takken T, Pisters MF. Factors associated with physical activity in patients with osteoarthritis of the hip or knee: a systematic review. Osteoarthritis Cartilage 2012;20:6–12.
12. Stubbs B, Hurley M, Smith T. What are the factors that influence physical activity participation in adults with knee and hip osteoarthritis? A systematic review of physical activity correlates. Clin Rehabil 2015;29:80–94.
13. White DK, Tudor-Locke C, Zhang Y, Niu J, Felson DT, Gross KD, et al. Prospective change in daily walking over two years in older

adults with or at risk of knee osteoarthritis: the MOST Study. Osteoarthritis Cartilage 2016;24:246–53.
14. Sallis JF, Saelens BE. Assessment of physical activity by self-report: status, limitations, and future directions. Res Q Exerc Sport 2000;71:1–14.
15. Prince SA, Adamo KB, Hamel ME, Hardt J, Connor Gorber S, Tremblay M. A comparison of direct versus self-report measures for assessing physical activity in adults: a systematic review. Int J Behav Nutr Phys Act 2008;5:56.
16. White DK, Tudor-Locke C, Zhang Y, Fielding R, LaValley M, Felson DT, et al. Daily walking and the risk of incident functional limitation in knee osteoarthritis: an observational study. Arthritis Care Res (Hoboken) 2014;66:1328–36.
17. Chmelo E, Nicklas B, Davis C, Miller GD, Legault C, Messier S. Physical activity and physical function in older adults with knee osteoarthritis. J Phys Act Health 2013;10:777–83.
18. Fukutani N, Iijima H, Aoyama T, Yamamoto Y, Hiraoka M, Miyanobu K, et al. Knee pain during activities of daily living and its relationship with physical activity in patients with early and severe knee osteoarthritis. Clin Rheumatol 2016;35:2307–16.
19. Song J, Chang AH, Chang RW, Lee J, Pinto D, Hawker G, et al. Relationship of knee pain to time in moderate and light physical activities: data from Osteoarthritis Initiative. Semin Arthritis Rheum 2018;47:683–8.
20. Detry MA, Ma Y. Analyzing repeated measurements using mixed models. JAMA 2016;315:407–8.
21. Altman R, Asch E, Bloch D, Bole G, Borenstein D, Brandt K, et al. Development of criteria for the classification and reporting of osteoarthritis: classification of osteoarthritis of the knee. Arthritis Rheum 1986;29:1039–49.
22. Roos EM, Lohmander LS. The Knee injury and Osteoarthritis Outcome Score (KOOS): from joint injury to osteoarthritis. Health Qual Life Outcomes 2003;1:64.
23. Bennell K, Dobson F, Hinman R. Measures of physical performance assessments: Self-Paced Walk Test (SPWT), Stair Climb Test (SCT), Six-Minute Walk Test (6MWT), Chair Stand Test (CST), Timed Up & Go (TUG), Sock Test, Lift and Carry Test (LCT), and Car Task. Arthritis Care Res (Hoboken) 2011;63 Suppl 11:S350–70.
24. Du HY, Newton PJ, Salamonson Y, Carrieri-Kohlman VL, Davidson PM. A review of the six-minute walk test: its implication as a self-administered assessment tool. Eur J Cardiovasc Nurs 2009;8:2–8.
25. Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. Ann Rheum Dis 1957;16:494–502.
26. Kessler S, Guenther KP, Puhl W. Scoring prevalence and severity in gonarthritis: the suitability of the Kellgren & Lawrence scale. Clin Rheumatol 1998;17:205–9.
27. Kothari M, Guermazi A, von Ingersleben G, Sieffert M, Block JE, Stevens R, et al. Fixed-flexion radiography of the knee provides reproducible joint space width measurements in osteoarthritis. Eur Radiol 2004;14:1568–73.
28. Song J, Semanik P, Sharma L, Chang RW, Hochberg MC, Mysiw WJ, et al. Assessing physical activity in persons with knee osteoarthritis using accelerometers: data in the Osteoarthritis Initiative. Arthritis Care Res (Hoboken) 2010;62:1724–32.
29. Hart TL, Swartz AM, Cashin SE, Strath SJ. How many days of monitoring predict physical activity and sedentary behaviour in older adults? Int J Behav Nutr Phys Act 2011;8:62.
30. Tudor-Locke C, Johnson WD, Katzmarzyk PT. Accelerometer-determined steps per day in US adults. Med Sci Sports Exerc 2009;41:1384–91.
31. Spadoni GF, Stratford PW, Solomon P, Wishart LR. The development and cross-validation of the P4: a self-report pain intensity measure. Physiother Canada 2003;55:32–40.
32. Spadoni GF, Stratford PW, Solomon PE, Wishart LR. The evaluation of change in pain intensity: a comparison of the P4 and single-item numeric pain rating scales. J Orthop Sport Phys Ther 2004;34:187–93.
33. Juhl C, Lund H, Roos EM, Zhang W, Christensen R. A hierarchy of patient-reported outcomes for meta-analysis of knee osteoarthritis trials: empirical evidence from a survey of high impact journals. Arthritis 2012;2012:136245.
34. Wang D, Jones MH, Khair MM, Miniaci A. Patient-reported outcome measures for the knee. J Knee Surg 2010;23:137–51.
35. Collins NJ, Prinsen CA, Christensen R, Bartels EM, Terwee CB, Roos EM. Knee Injury and Osteoarthritis Outcome Score (KOOS): systematic review and meta-analysis of measurement properties. Osteoarthritis Cartilage 2016;24:1317–29.
36. Robbins SM, Rastogi R, Howard J, Rosedale R. Comparison of measurement properties of the P4 pain scale and disease specific pain measures in patients with knee osteoarthritis. Osteoarthritis Cartilage 2014;22:805–12.
37. Buchowski MS, Choi L, Majchrzak KM, Acra S, Charles E, Chen KY. Seasonal changes in amount and patterns of physical activity in women. J Phys Act Heal 2009;6:252–61.
38. Witham MD, Donnan PT, Vadiveloo T, Sniehotta FF, Crombie IK, Feng Z, et al. Association of day length and weather conditions with physical activity levels in older community dwelling people. PLoS One 2014;9:e85331.
39. Stevenson JD, Roach R. The benefits and barriers to physical activity and lifestyle interventions for osteoarthritis affecting the adult knee. J Orthop Surg Res 2012;7:15.
40. Hammett T, Simonian A, Austin M, Butler R, Allen KD, Ledbetter L, et al. Changes in physical activity after total hip or knee arthroplasty: a systematic review and meta-analysis of six- and twelve-month outcomes. Arthritis Care Res (Hoboken) 2018;70:892–901.
41. Roddy E, Zhang W, Doherty M, Arden NK, Barlow J, Birrell F, et al. Evidence-based recommendations for the role of exercise in the management of osteoarthritis of the hip or knee–the MOVE consensus. Rheumatology (Oxford) 2005;44:67–73.
42. Talbot LA, Gaines JM, Huynh TN, Metter EJ. A home-based pedometer-driven walking program to increase physical activity in older adults with osteoarthritis of the knee: a preliminary study. J Am Geriatr Soc 2003;51:387–92.
43. Callahan LF, Shreffler JH, Altpeter M, Schoster B, Hootman J, Houenou LO, et al. Evaluation of group and self-directed formats of the arthritis foundation's Walk With Ease program. Arthritis Care Res (Hoboken) 2011;63:1098–107.
44. Stratford PW, Dogra M, Woodhouse L, Kennedy DM, Spadoni GF. Validating self-report measures of pain and function in patients undergoing hip or knee arthroplasty. Physiother Canada 2009;61:189–94.
45. Zhaoyang R, Martire LM, Sliwinski MJ. Morning self-Efficacy predicts physical activity throughout the day in knee osteoarthritis. Heal Psychol 2017;36:568–76.
46. Murphy SL, Kratz AL, Williams DA, Geisser ME. The association between symptoms, pain coping strategies, and physical activity among people with symptomatic knee and hip osteoarthritis. Front Psychol 2012;3:326.
47. Murphy SL, Schepens Niemiec S, Lyden AK, Kratz AL. Pain, fatigue, and physical activity in osteoarthritis: the moderating effects of pain- and fatigue-related activity interference. Arch Phys Med Rehabil 2016;97:S201–9.
48. Dunlop DD, Song J, Semanik PA, Sharma L, Chang RW. Physical activity levels and functional performance in the Osteoarthritis Initiative: a graded relationship. Arthritis Rheum 2011;63:127–36.

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Objectively Assessed Foot and Ankle Characteristics in Patients With Systemic Lupus Erythematosus: A Comparison With Age- and Sex-Matched Controls

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Objective. To objectively identify foot and ankle characteristics in patients with systemic lupus erythematosus (SLE) compared to age- and sex-matched controls.

Methods. A total of 54 patients with SLE and 56 control participants attended a study visit designed to comprehensively assess the foot and ankle. Objectively assessed foot characteristics included muscle strength, joint motion, foot posture, foot problems, protective sensation, vibration perception threshold (VPT), ankle brachial index (ABI), plantar pressure, and spatiotemporal gait characteristics. Self-reported measure of foot pain and impairment were also assessed using a 100-mm foot pain visual analog scale. Data were analyzed using regression models. Plantar pressure and gait models were adjusted for walking velocity, body mass index, and foot pain.

Results. Compared to controls, participants with SLE had lower muscle force for plantarflexion, dorsiflexion, inversion, and eversion (all $P < 0.001$), higher foot posture indices ($P = 0.007$), higher foot problem scores ($P = 0.001$), higher VPT ($P = 0.001$), and more frequent abnormal ABI (odds ratio [OR] 3.13, $P = 0.044$). Participants with SLE also had lower peak pressure and higher pressure time integrals for all foot regions (all $P < 0.001$), lower step and stride length, velocity, and cadence, and higher step, swing, stance, and single and double support times compared to controls (all $P < 0.001$). Compared to controls, participants with SLE also reported greater foot pain ($P < 0.001$).

Conclusion. Patients with SLE experience a wide range of foot symptoms. This study has provided objective evidence of foot and ankle disease in patients with SLE, including reduced muscle strength and altered gait patterns when compared to controls. This highlights the importance of foot health assessments as part of SLE management.

INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune rheumatic disease characterized by multiorgan involvement (1). The clinical presentation of SLE is diverse, with manifestations in the cutaneous, musculoskeletal, cardiovascular, and neurologic systems (1). Patients with SLE report a decreased health-related quality of life with associated chronic fatigue, activity limitation, and reduced functional capacity (2,3).

The feet have been identified as an underappreciated area of involvement in patients with SLE (4). A greater prevalence of sonographically evident inflammatory joint abnormalities has been reported in the feet compared to the hands and wrists (5). The degree of foot symptoms reported by patients with SLE has been highlighted in survey studies (6,7) and includes joint pain and swelling, impaired circulation, compromised skin and nail health, and foot deformity. Patients with SLE also report foot- and leg-related functional impairment and activity limitation (6–8). More than one-third of patients with SLE report either difficulty or a complete inability to walk (7). However, objectively assessed measures of foot function, including muscle strength and gait characteristics, have not been previously evaluated in patients with SLE. Objective podiatric assessments can be undertaken efficiently and quickly in clinical practice to determine the foot health status of patients. Such assessments are central in identifying the needs of the patient and informing treatment strategies to prevent and manage foot problems.

Further research that assesses objective foot and ankle characteristics is warranted to quantify the extent and nature of foot problems experienced by patients with SLE. This study aimed to identify foot and ankle characteristics in patients with SLE compared to age- and sex-matched control participants.

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No potential conflicts of interest relevant to this article were reported.

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SIGNIFICANCE & INNOVATIONS

- This was the first study to comprehensively assess objective foot and ankle characteristics in patients with systemic lupus erythematosus (SLE).
- Patients with SLE exhibit structural and functional evidence of foot disease, including reduced muscle strength, when compared to controls.
- Patients with SLE demonstrated altered gait patterns, including reduced gait velocity, even after adjusting for foot pain.

PATIENTS AND METHODS

Participants. A cross-sectional observational study was undertaken. All participants were recruited from Auckland, New Zealand. Participants with SLE were recruited from secondary care rheumatology clinics in Counties Manukau and Waitemata District Health Boards in Auckland and had a physician diagnosis of SLE according to the 2012 Systemic Lupus International Collaborating Clinics criteria (9). Participants with SLE were excluded if they had cutaneous lupus without systemic involvement. Age- (within 5 years) and sex-matched control participants were recruited from Auckland University of Technology (AUT) staff through poster and newsletter advertising. Participants in both groups were excluded if they were younger than 20 years of age (legal minors), required an interpreter, had recent foot surgery or trauma, or had neuromuscular or other arthritic inflammatory conditions. All participants provided written informed consent prior to data collection. Ethical approval was obtained from AUT Ethics Committee (AUTEC 16/209).

Demographic and clinical assessment. Participants attended a single clinical visit at AUT, New Zealand. Demographic data were obtained, and a swollen and tender joint count (66 and 68 joints assessed) (10) was completed on all participants. Disease characteristics were recorded for participants with SLE, including disease duration, disease activity using the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) (11), medication, comorbidities, and, if available, recent laboratory results within 4 months before the study visit (creatinine, erythrocyte sedimentation rate, and C-reactive protein level).

Assessment of musculoskeletal foot characteristics. A single experienced podiatric researcher (SS), who was not blinded to the participant's group allocation, undertook all objective assessments. Isometric muscle force for ankle plantarflexion, dorsiflexion, inversion, and eversion was measured using a CITEC hand-held dynamometer (CIT Technics) (12). Participants were seated during testing with hips flexed and knees extended. The examiner stabilized the lower leg and foot in a neutral position. Three consecutive contractions of 3 to 5 seconds were recorded for each muscle group using the make technique, in which the examiner holds the dynamometer stationary while the participant exerts maximal external force against it. The dynamometer was positioned proximal to the metatarsophalangeal joints on the plantar aspect of the foot for plantarflexion or on the dorsum of the foot for dorsiflexion; on the medial aspect of the first metatarsal shaft for inversion; and on the lateral aspect of the fifth metatarsal shaft for eversion. The maximum of the 3 measurements for each foot was used in the analysis.

Range of motion for dorsiflexion of the first metatarsophalangeal (MTP) joint was assessed using a hand-held goniometer (13). Participants were positioned seated with knees extended, and the shafts of the first metatarsal and proximal phalanx were marked. The goniometer was aligned with the center of the joint, and a passive dorsiflexion force was applied to the hallux up to its end range of motion. Ankle inversion and eversion were assessed with participants seated and knees extended (14). The examiner located and marked the midline of the anterior lower leg and the longitudinal midline of the second metatarsal, with the center of the goniometer positioned at the anterior ankle. With the ankle in a relaxed position, the examiner guided the participant to their end range for eversion and inversion. Ankle dorsiflexion was assessed using the weight-bearing lunge test (15). Participants were positioned with their tested foot over a line drawn perpendicular to a wall, with the center of their heel and second toe positioned over the line. They were instructed to lunge forward so their knee touched a vertical line drawn on the wall while ensuring that their heel remained in contact with the floor. The examiner measured the angle between the anterior tibia and the wall. The average of 3 measurements for each foot were used for analysis.

Foot type was assessed using the Foot Posture Index (FPI) (16), which has demonstrated moderate intrarater reliability for the assessment of foot posture in adults (17). During assessment, participants were instructed to stand in a relaxed weight-bearing position while the examiner made observations of the hindfoot and forefoot based on 6 criteria. Each FPI criterion was scored on a 5-point scale (–2 to +2). The scores for the 6 criteria are summated to give an overall score for each foot, ranging from –12 (highly supinated) to +12 (highly pronated).

The presence of foot problems was determined using the Foot Problem Score (18), which covers foot pain, foot deformity, and skin lesions. Foot pain was dichotomized as yes (5 points) or no (0 points); hallux valgus was graded as mild (1 point), moderate (2 points), or severe (3 points); lesser toe deformities including hammer and claw toes, hyperkeratotic lesions including corns and calluses, and other bony prominences including tailor's bunions and exostoses were each scored 1 point (18). Points for each foot were summated to give a total score for each participant.

Assessment of plantar pressure and spatiotemporal gait parameters. Dynamic plantar pressure was captured during barefoot walking using a MatScan system (Tekscan) and a 2-step gait initiation protocol, which required the participant to step on a platform on their second step and to continue walking past the platform for at least 2 more steps. Research Foot, version 6.61 (TekScan) was used to mask the plantar foot into the heel, midfoot, first metatarsal, second metatarsal, metatarsals 3 to 5, the hallux and the lesser toes (19), and peak plantar pressure (kPa) and pressure time integrals (kPa*s) were computed for each region. Means were computed from 3 repeated trials for each foot.

Spatial and temporal parameters during barefoot walking were collected using a 4.88 × 0.61 meters electronic GAITRite walkway system (CIR Systems). Participants were instructed to walk at a comfortable walking speed (20). Prior to calculation of the gait parameters, the data were reviewed on the monitor screen to ensure that footfalls had been correctly identified. The GAITRite software (GAITRite gold, version 3.2b) was used to compute the following parameters: velocity, cadence, step and stride length, support base, and step, swing, stance, and single and double support times. Means were computed from the 3 repeated walking trials for each parameter.

Assessment of neurovascular foot characteristics. Protective sensation of the plantar foot was assessed using a 10-gram monofilament using a 3-site testing protocol (hallux, third metatarsal head, fifth metatarsal head) (21). Each site was assessed once, and loss of sensation for each foot was defined as an inability to detect the monofilament at >1 site (21). Vibration perception was assessed using a biothesiometer placed on the dorsal hallux proximal to the nail fold. The amplitude was increased at an even rate from 0 mV, and the participant was asked to indicate when they felt the vibratory stimuli. The average of 3 measurements for each foot was used for the analysis. A loss of vibratory perception was defined as a threshold of >25 mV (22).

Skin temperature was assessed using a DermaTemp infrared thermometer (Exergen Corporation). The average temperature from the plantar first, third, and fifth metatarsal heads was recorded. The average of 3 repetitions for each foot was used for the analysis.

The ankle brachial index (ABI) was used to determine the presence of peripheral arterial disease. Participants rested for >5 minutes in a supine position before testing. Systolic pressure of the dorsalis pedis, posterior tibial, and brachial arteries was determined bilaterally using an 8-MHz Doppler probe and sphygmomanometer. The higher of the 2 brachial arteries was divided by the highest ankle pressure for each side. The lower of the 2 values was used for analysis. An ABI value of ≤1.00 was considered abnormal and indicative of occlusive disease (23).

Assessment of patient-reported pain and disability. Right and left foot pain during the previous week was assessed using 100-mm visual analog scales (VAS) anchored with no pain at the left and extreme pain at the right. Region-specific foot pain was also assessed by having participants indicate the areas of pain experienced on each foot by shading in areas on validated diagrams (24). The diagrams were divided into 10 regions (first MTP joint, hallux, great toe, lesser toes, plantar forefoot, midfoot, medial arch, ankle, plantar heel, and posterior heel). The presence of pain was recorded for each region as present (scored 1) or absent (scored 0). The 10 regions were further stratified into: toes, forefoot, midfoot, and hindfoot.

Disabling foot pain was assessed using the Manchester Foot Pain and Disability Index (MFPDI) (25), which is a 19-item index measuring foot-related functional limitation, pain, and physical appearance. Statements relating to each item were answered none of the time (scored 0), on some days (scored 1), or on most/everyday(s) (scored 2) in the previous month. A total score of 38 was calculated for each participant. The Lower Limb Task Questionnaire (LLTQ) (26) was used to measure leg function. The LLTQ consists of 2 sections, one related to activities of daily living and the other to recreational activities. Each section includes 10 activities for which participants are asked to rate the difficulty they have had with each in the preceding 24 hours (where unable = 0, severe difficulty = 1, moderate difficulty = 2, mild difficulty = 3, and no difficulty = 4).

Table 1. Demographic and clinical characteristics*

	Controls (n = 56)	SLE (n = 54)	*P*
Age, years	48 ± 14	52 ± 14	0.21
Female sex, no. (%)	52 (93)	50 (93)	0.97
Ethnicity, no. (%)			0.08
European	41 (73)	31 (57)	
Māori	3 (5)	3 (6)	
Pacific	0 (0)	5 (9)	
Asian	12 (21)	13 (24)	
Other	0 (0)	2 (4)	
Weight, kg	67.3 ± 12.1	74.6 ± 19.5	0.020†
Height, meters	1.64 ± 0.07	1.63 ± 0.08	0.30
Body mass index, kg/m^2	24.87 ± 4.11	28.10 ± 7.19	0.004†
Systolic blood pressure, mm Hg	115 ± 14	120 ± 19	0.11
Diastolic blood pressure, mm Hg	74 ± 10	76 ± 9	0.31
Smoker, no. (%)			0.046†
Never	45 (80)	33 (61)	
History	9 (16)	13 (24)	
Current	2 (4)	8 (15)	
Employment, no. (%)			0.006†
Employed	39 (70)	32 (59)	
Not working	3 (5)	14 (26)	
Retired	5 (9)	6 (11)	
Student	9 (16)	2 (4)	
Tender joint count	0.7 ± 1.8	8.2 ± 9.5	<0.001†
Swollen joint count	0.3 ± 1.1	2.8 ± 8.1	0.025†

* Values are mean ± SD unless indicated otherwise. SLE = systemic lupus erythematosus.
† Significant at $P < 0.05$.

Statistical analysis. A total sample size of 112 participants was computed for this study (56 participants with SLE and 56 age- and sex-matched controls). This sample size was calculated based on previous studies that measured foot pain using a 100-mm VAS in patients with another autoimmune rheumatic disease (rheumatoid arthritis) (27). These studies assumed the mean ± SD values for foot pain as 35.3 ± 22.9 mm for participants with autoimmune disease and 20.5 ± 24.9 mm in controls. The power was set to 0.90, and the level of significance 0.05. Due to time constraints within the project, 54 participants with SLE and 56 controls were ultimately recruited.

All raw data were described separately for each group as number (percentage) for categorical data and mean ± SD for continuous data. Continuous outcomes were reviewed for normality using visual inspections (histograms, Q–Q plots, and scatterplots) and formal tests (Kolmogorov-Smirnov and Shapiro-Wilk). Linear regression (continuous outcome measures), multinomial logistic regression (ordinal data), and binary logistic regression (dichotomous data) were used to determine the difference in outcome measures between the 2 groups. Where appropriate, the models accounted for repeated measures taken from right and left feet through a mixed-modeling approach in which a participant-specific random effect and participant-nested random effect for foot side were included (28). This analysis produces results identical to an analysis of measures averaged for each foot side that would allow for a correlation between foot sides (28). Due to the potential influence of foot pain on objective measures of structure and function, the regression models for muscle force, joint motion, FPI, plantar pressure, and gait characteristics were adjusted for foot pain VAS. In addition, plantar pressure was adjusted for body mass index (BMI) and gait velocity, and spatiotemporal parameters were adjusted for BMI (due to the linear relationship between increased plantar pressure and increases in BMI and gait velocity). All hypothesis tests (excluding covariate testing) were carried out at a 5% level of significance against 2-sided alternatives. No adjustment for multiplicity was used, but all test statistics, their null distributions, and their observed significance levels were reported. Data were analyzed using SPSS Statistics, version 24.

RESULTS

Participants. Invitation letters were sent to 448 patients with SLE. Of these, 65 registered interest in the study. Eleven did not fulfill the inclusion criteria, leaving 54 participants with SLE to complete the study. A total of 56 age- and sex-matched control subjects also completed the study. The majority of participants were middle-aged women of European ethnicity (Table 1). Compared to controls, participants with SLE had a significantly higher BMI ($P = 0.004$), were more likely to have a history of smoking ($P = 0.046$) or be unemployed ($P = 0.006$), and had a higher tender joint count ($P < 0.001$) and swollen joint count ($P = 0.025$). Disease characteristics for participants with SLE are presented in Table 2. Participants with SLE had a mean ± SD SLEDAI-2K score of 13.3 ± 9.7 and disease duration of 15 ± 12 years.

Musculoskeletal foot characteristics. Differences in musculoskeletal foot characteristics between groups are presented in Table 3. Compared to controls, participants with SLE had significantly lower muscle force for plantarflexion, dorsiflexion, and inversion and eversion of the ankle (all $P < 0.001$). Participants with SLE also had a significantly higher FPI, which is indicative of a more pronated foot posture ($P = 0.007$) and a greater Foot Problem Score ($P = 0.001$). There were no differences between groups for joint motion, hallux valgus, or other deformities (all $P > 0.05$).

Plantar pressure and spatiotemporal gait parameters. Table 4 presents the differences between groups for plantar pressure, pressure time integrals, and spatiotemporal parameters. After adjusting for BMI and gait velocity, participants with SLE had significantly lower peak pressure

Table 2. SLE disease characteristics (n = 54)*

Characteristics	Values
SLEDAI-2K score, mean ± SD	13.3 ± 9.7
SLE disease duration, mean ± SD years	15 ± 12
Laboratory tests, mean ± SD	
CRP level, mg/liter	6.8 ± 10.7
ESR, mm/hour	35.4 ± 41.1
Creatinine, μmol/liter	76.8 ± 25.8
Medications	
Hydroxychloroquine	32 (59)
Immunosuppressants	21 (39)
Prednisone	19 (35)
NSAIDs	16 (30)
Analgesics	17 (31)
Anticoagulants	5 (9)
Statins	8 (15)
Antihypertensives	13 (24)
Comorbidities and complications of disease	
Lupus nephritis	8 (15)
Chronic kidney disease	2 (4)
Raynaud's syndrome	21 (39)†
Fibromyalgia	4 (7)
Sjögren's syndrome	6 (11)
Chilblain lupus	24 (44)‡
Osteoporosis	7 (13)
Depression	3 (6)
Dyslipidemia	6 (6)
Cardiovascular diseases	6 (6)
Hypertension	17 (31)
Diabetes mellitus	1 (2)

* Values are no. (%) unless indicated otherwise. SLE = systemic lupus erythematosus; SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index 2000; CRP = c-reactive protein; ESR = erythrocyte sedimentation rate; NSAIDs = nonsteroidal antiinflammatory drugs.
† Involving feet 14 (26%).
‡ Involving feet 19 (35%).

Table 3. Differences in musculoskeletal foot characteristics between controls and patients with SLE*

	Controls	SLE	Diff. (95% CI)	OR (95% CI)	*P*
Plantarflexion force, N†	232.0 ± 79.7	188.9 ± 70.9	−43.1 (−63.2, −23.1)		<0.001‡
Dorsiflexion force, N†	177.0 ± 60.4	145.1 ± 53.2	−32.0 (−47.1, −16.8)		<0.001‡
Inversion force, N†	103.1 ± 44.7	78.1 ± 40.7	−25.0 (−36.4, −13.6)		<0.001‡
Eversion force, N	90.0 ± 34.9	66.6 ± 31.9	−23.4 (−32.3, −14.5)		<0.001‡
First MTP joint dorsiflexion, ROM degrees†	79.7 ± 25.7	80.6 ± 22.7	0.9 (−5.5, 7.4)		0.77
STJ inversion, ROM degrees†	36.0 ± 17.4	35.1 ± 13.3	−0.9 (−5.0, 3.2)		0.67
STJ eversion, ROM degrees†	13.8 ± 9.5	14.0 ± 8.2	0.2 (−2.2, 2.6)		0.87
Ankle lunge, degrees†	43.3 ± 10.5	40.9 ± 9.8	−2.3 (−5.0, 0.4)		0.09
Foot posture index†	3.8 ± 5.3	5.6 ± 5.1	1.8 (0.5, 3.2)		0.009‡
Foot problem score	11.3 ± 7.3	16.3 ± 8.6	5.0 (2.0, 8.0)		0.001‡
Foot tenderness present, no. (%)	14 (13)	67 (62)		14.32 (6.41, 32.00)	<0.001‡
Foot swelling present, no. (%)	9 (8)	30 (28)		4.58 (1.78, 11.76)	0.002‡
Hallux valgus grade, no. (%)				0.95 (0.57, 1.57)	0.84
None	60 (54)	78 (72)			
Mild	30 (27)	18 (17)			
Moderate	15 (13)	8 (7)			
Severe	7 (6)	2 (2)			
Tinea, no. (%)	4 (4)	5 (5)		1.16 (0.36, 3.78)	0.81
Verruca, no. (%)	0 (0)	3 (3)		1.58 (0.37, 6.69)	0.53
Digital amputation, no. (%)	0 (0%)	2 (2%)		1.37 (0.31, 6.04)	0.68
Bony prominence(s), no. (%)	35 (31)	27 (25)		0.72 (0.36, 1.46)	0.36
Hammer toes, no. (%)	9 (8)	6 (6)		0.74 (0.27, 2.07)	0.57
Claw toes, no. (%)	14 (13)	14 (13)		1.04 (0.39, 2.77)	0.93
Hyperkeratotic lesions, no. (%)	98 (88)	91 (84)		0.75 (0.30, 1.86)	0.53

* Values are mean ± SD unless indicated otherwise. No. (%) calculated from no. of feet (control = 112 feet, SLE = 108 feet). SLE = systemic lupus erythematosus; Diff. = difference between controls and patients with SLE; 95% CI = 95% confidence interval; OR = odds ratio; N = newtons; MTP = metatarsophalangeal; ROM = range of motion; STJ = subtalar joint.
† Adjusted for foot pain visual analog scale.
‡ Significant at $P < 0.05$.

and significantly higher pressure-time integrals at all 7 regions of the plantar foot (all $P < 0.001$). After adjusting for BMI, participants with SLE had significantly lower step and stride length and higher step, swing, stance, and single and double support times compared to controls (all $P < 0.001$). Participants with SLE also had a significantly lower velocity and cadence compared to controls (all $P < 0.001$).

Neurovascular foot characteristics. Table 5 presents the differences between groups for the neurovascular characteristics. Participants with SLE had significantly higher vibration perception threshold (VPTs), indicative of reduced vibratory perception ($P = 0.001$), and were more likely to have abnormal ABI (odds ratio [OR] 3.13, $P = 0.044$). No differences were observed between groups for the remaining neurovascular measures (all $P > 0.05$).

Patient-reported pain and disability. Table 6 presents the differences in patient-reported outcomes between groups. Compared to controls, participants with SLE reported significantly worse foot pain VAS ($P < 0.001$), MFPDI ($P < 0.001$), and LLTQ ($P < 0.001$) scores. Participants with SLE were more likely to have foot pain compared to controls (62% versus 29%, OR 4.31; $P < 0.001$). The most common individual sites for foot pain in SLE were the lesser toes (n = 41 feet, 38%), dorsal midfoot (n = 40 feet, 37%), and ankle (n = 34 feet, 32%). The hindfoot was the most common overall region for foot pain in patients with SLE (n = 47 feet, 44%). Forty-six feet (43%) of participants with SLE had pain in >2 regions.

DISCUSSION

The multisystem heterogenic nature of SLE is reflected in the diversity of structural, functional, and neurovascular foot problems observed in the current study, including impaired foot and ankle muscle function and gait changes, which have not been assessed previously in this population. Patients with SLE also report a range of foot- and ankle-related problems, including wide-spread pain, functional disability, and activity limitations.

The reductions in plantarflexion, dorsiflexion, inversion, and eversion muscle force observed in the current study are similar to those in previous studies when assessing the function of major leg muscle groups in patients with SLE, including quadriceps and hamstrings (3,29,30). Foot and ankle muscle strength is important in performing daily functional activities, including walking, which requires adequate sagittal plane motion for forward progression and frontal plane motion for stability and shock absorption (31). Muscle weakness in SLE may be due to a reduction in physical fitness as a consequence of fatigue, a symptom experienced by 80% of patients with SLE (2).

Results from the current study showed reduced peak pressures and increased pressure time integrals in all areas of the

Table 4. Difference in plantar pressure and spatiotemporal gait parameters between controls and patients with SLE*

	Controls	SLE	Diff.	(95% CI for diff.)	*P*
Peak plantar pressure, kPa†					
Heel	244.0 ± 111.0	155.4 ± 87.4	−88.6	(−115.2, 62.0)	<0.001‡
Midfoot	116.1 ± 68.6	68.3 ± 55.3	−47.8	(−64.4, −31.3)	<0.001‡
First metatarsal	209.3 ± 90.6	119.0 ± 70.9	−90.3	(−112.0, −68.7)	<0.001‡
Second metatarsal	278.8 ± 104.1	174.0 ± 80.7	−104.7	(−129.5, −79.9)	<0.001‡
Third to fifth metatarsals	235.3 ± 88.8	149.4 ± 66.9	−86.0	(−106.9, 65.0)	<0.001‡
Hallux	189.0 ± 100.2	127.2 ± 79.6	−61.8	(−85.9, −37.8)	<0.001‡
Toes	124.1 ± 82.6	63.6 ± 89.3	−60.5	(−80.8, −40.1)	<0.001‡
Pressure time integral, kPa × seconds interaction†					
Heel	46.4 ± 61.2	154.5 ± 45.3	108.1	(93.8, 122.4)	<0.001‡
Midfoot	25.3 ± 34.9	64.5 ± 26.0	39.3	(31.1, 47.4)	<0.001‡
First metatarsal	50.6 ± 66.7	120.4 ± 51.4	69.8	(53.9, 85.6)	<0.001‡
Second metatarsal	73.6 ± 64.2	176.2 ± 47.8	102.6	(87.5, 117.7)	<0.001‡
Third to fifth metatarsals	56.6 ± 58.4	146.1 ± 43.6	89.5	(75.8, 103.2)	<0.001‡
Hallux	36.1 ± 56.2	128.6 ± 42.0	92.5	(79.3, 105.7)	<0.001‡
Toes	26.1 ± 35.7	60.9 ± 28.0	34.8	(26.3, 43.4)	<0.001‡
Spatiotemporal gait parameters§					
Step length, cm	63.7 ± 102	57.2 ± 9.5	−6.5	(−9.1, −3.9)	<0.001‡
Stride length, cm	127.6 ± 20.0	114.7 ± 19.1	−12.9	(−18.1, −7.7)	<0.001‡
Support base, cm	9.8 ± 4.0	10.3 ± 3.7	0.5	(−0.6, 1.5)	0.37
Step time, seconds	0.52 ± 0.08	0.58 ± 0.08	0.06	(0.04, 0.08)	<0.001‡
Swing time, seconds	0.39 ± 0.04	0.41 ± 0.04	0.02	(0.01,0.03)	<0.001‡
Stance time, seconds	0.64 ± 0.13	0.73 ± 0.12	0.10	(0.06, 0.13)	<0.001‡
Single support time, seconds	0.39 ± 0.05	0.42 ± 0.04	0.02	(0.01, 0.04)	<0.001‡
Double support time, seconds	0.24 ± 0.10	0.31 ± 0.09	0.07	(0.05, 0.10)	<0.001‡
Velocity, cm/second	125.1 ± 24.5	102.1 ± 19.8	−23.0	(−31.4, −14.6)	<0.001‡
Cadence, steps/minute	117.9 ± 13.5	105.7 ± 10.9	−12.2	(−16.9, −7.6)	<0.001‡

* Values are mean ± SD unless indicated otherwise. SLE = systemic lupus erythematosus; Diff. = difference between controls and patients with SLE; 95% CI = 95% confidence interval.
† Adjusted for body mass index, gait velocity, and foot pain visual analog scale.
‡ Significant at $P < 0.05$.
§ Adjusted for body mass index and foot pain visual analog scale.

plantar foot in patients with SLE. These results suggest that even though maximal load at each area under the foot in patients with SLE is low, relative to that of control participants, the cumulative effect of pressure over time is very high. High pressure time integrals are associated with underlying tissue damage and pain in other patient populations, including those with diabetes mellitus (32) and rheumatoid arthritis (33). Although this is most commonly considered a result of a slow walking speed or the presence of foot pain (34,35), the current analysis adjusted for gait velocity and foot pain, meaning that the findings may be attributed to factors beyond these factors. It is possible that alterations in foot structure and posture, as well as changes to foot function resulting from muscle strength deficits and reduced sensation, may contribute to these altered gait patterns in patients with SLE.

Limitations to foot joint motion were not a characteristic feature in patients with SLE in the current study. This may reflect the infrequency of sonographic and radiographic foot joint and bone lesions in patients with SLE (36,37) and the nonerosive nature of

Table 5. Differences in neurovascular foot characteristics between controls and patients with SLE*

	Controls	SLE	Diff. (95% CI)	OR (95% CI)	*P*
VPT, mV	8.9 ± 9.4	13.2 ± 9.5	4.3 (1.8, 6.8)		0.001†
Temperature, °C	24.9 ± 3.0	25.2 ± 2.9	0.5 (−0.5, 1.1)		0.44
Ankle brachial index	1.03 ± 0.06	1.02 ± 0.14	−0.01 (−0.05, 0.03)		0.61
Loss of protective sensation, no. (%)‡	3 (3)	10 (9)		2.89 (0.75, 6.97)	0.11
Abnormal VPT (< 25 mV), no. (%)‡	0 (0)	10 (9)		3.56 (0.98, 12.91)	0.05
Intermittent claudication, no. (%)	0 (0)	1 (2)		1.37 (0.17, 11.30)	0.77
Abnormal ABI, no. (%)	5 (9)	13 (24)		3.13 (1.03, 9.49)	0.044†

* Values are mean ± SD unless indicated otherwise. SLE = systemic lupus erythematosus; Diff. = difference between controls and patients with SLE; 95% CI = 95% confidence interval; OR = odds ratio; VPT = vibration perception threshold; ABI = ankle brachial index.
† Significant at $P < 0.05$.
‡ Calculated from no. of feet (control = 112 feet, SLE = 108 feet).

Table 6. Difference in self-reported pain and disability between controls and patients with SLE*

	Controls	SLE	Diff. (95% CI)	OR (95% CI)	*P*
Foot pain VAS score, mean ± SD, mm	4.5 ± 24.3	25.7 ± 23.9	21.2 (14.6, 27.7)		<0.001†
MFPDI score, total mean ± SD	1.3 ± 2.6	11.6 ± 8.4	10.31 (8, 12.6)		<0.001†
LLTQ activities of daily living score, mean ± SD	39.2 ± 1.4	34.7 ± 5.6	−4.57 (−6.1, −3)		<0.001†
LLTQ recreational activities score, mean ± SD	35.7 ± 11.0	24.9 ± 6.2	−10.79 (−14.1, −7.4)		<0.001†
Any foot pain present	32 (29)	67 (62)		4.31 (2.24, 8.29)	<0.001†
First MTP joint pain	12 (11)	25(23)		2.51 (1.08, 5.88)	0.034†
Hallux pain	9 (8)	22 (20)		2.93 (1.13, 7.61)	0.027†
Great toe pain	17 (15)	32 (30)		2.39 (1.10, 5.26)	0.028†
Lesser toe pain	13 (12)	41 (38)		4.85 (2.17, 10.84)	<0.001†
Plantar forefoot pain	9 (8)	24 (22)		3.29 (1.29, 8.38)	0.013†
Dorsal midfoot pain	7 (6)	40 (37)		9.03 (3.52, 23.12)	<0.001†
Medial arch pain	3 (3)	19 (18)		4.64 (1.65, 13.06)	0.004†
Ankle pain	9 (8)	34 (32)		5.46 (2.23, 13.40)	<0.001†
Plantar heel pain	1 (1)	16 (15)		5.03 (1.57, 16.14)	0.007†
Posterior heel pain	5 (5)	20 (19)		4.84 (1.58, 14.81)	0.006†
Any toe pain	17 (15)	43 (40)		3.85 (1.82, 8.15)	<0.001†
Any forefoot pain	15 (13)	32 (30)		2.76 (1.27, 6.01)	0.011†
Any midfoot pain	7 (6)	39 (36)		8.67 (3.37, 22.32)	<0.001†
Any hindfoot pain	9 (8)	47 (44)		9.56 (3.89, 23.50)	<0.001†
Pain ≥ 2 locations‡	12 (11)	46 (43)		6.11 (2.79, 13.42)	<0.001†
Pain ≥ 3 locations‡	3 (3)	32 (30)		15.18 (4.11, 46.04)	<0.001†

* Values are no. (%) unless indicated otherwise. No. (%) calculated from no. of feet (control = 112 feet, SLE = 108 feet). SLE = systemic lupus erythematosus; diff. = difference between controls and patients with SLE; 95% CI = 95% confidence interval; OR = odds ratio; VAS = visual analog scale; MFPDI = Manchester Foot Pain and Disability Index; LLTQ = Lower Limb Task Questionnaire; MTP = metatarsophalangeal.
† Significant at $P < 0.05$.
‡ From either toes, forefoot, midfoot, and/or hindfoot.

SLE arthritis (38). Similar rates of bony deformities, including hallux valgus and clawed digits, as well as skin lesions and hyperkeratosis, were also observed between patients with SLE and controls. This is consistent with a previous study that found that the prevalence of hallux valgus in SLE was not different from controls (37).

Consistent with previous research (39), the current study found greater vibration perception thresholds in patients with SLE in comparison to controls, indicating impaired large peripheral nerve fiber function. Nerve conduction studies have also shown significant deterioration of leg motor and sensory nerves in patients with SLE (39,40). Finally, almost one-fourth of participants in the current study had abnormal ABI values. Peripheral vascular disease is fairly prevalent in patients with SLE (41–43), resulting in decreased blood flow to the extremities and accounting for the high occurrence of chilblain lupus and Raynaud's phenomenon in this population (44).

The results of the current study highlight the extent and magnitude of self-reported foot pain and disability experienced by patients with SLE. Previous research has reported a prevalence of current self-reported foot pain in patients with SLE ranging from 33% to 66% (6,7,37). Consistent with this previous research, 62% of participants with SLE in the current study reported foot pain. Although foot pain was widespread and often affected multiple locations, the most common area for pain in patients with SLE was the hindfoot; also consistent with previous postal survey data (6,7). Although the exact cause of this pattern of pain is unclear, joints of the hindfoot have been reported to have more frequent synovitis on ultrasound imaging in patients with SLE compared to controls (37).

There are some limitations to our study. First, the participants with SLE in the current study were recruited from secondary care clinics in Auckland, New Zealand and may not represent SLE in rural communities or globally. Although control participants and participants with SLE were recruited from the same city, they may not have come from the same source population, which may have increased the risk for selection bias. In addition, gait characteristics were assessed during barefoot walking, which may not reflect patterns typically exhibited in daily activity with the use of everyday footwear. Furthermore, the potential for outcome ascertainment bias may have been introduced since the podiatric researcher was not blinded to the group allocation of the participants and therefore may have influenced the strength of differences between groups. Finally, patients with foot problems may have been more interested in a study of foot disease, which may lead to overestimation of the prevalence of foot problems in patients with SLE.

These results highlight the importance of foot health assessments as part of the management of patients with SLE. Existing studies have shown that podiatric services, including nail and skin care, clinical padding, foot orthoses, and footwear advice for patients who have rheumatic foot conditions, such

as rheumatoid arthritis, gout, and other connective tissues diseases, are effective in reducing foot pain, impairment, and disability (45). Furthermore, previous work has shown that patients with SLE wear shoes that are inappropriate for their level of pain and disability (46). Along with the results from the current study, these findings warrant the need for further research that assesses the role of foot-specific interventions, including general podiatric care and footwear.

In conclusion, patients with SLE exhibit objective evidence of foot and ankle disease, including reduced foot and ankle muscle strength and altered plantar pressure and gait patterns, when compared to matched controls. Patients with SLE also report a wide range of foot symptoms related to pain, disability, and activity limitation.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Stewart had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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REFERENCES

1. D'Cruz DP, Khamashta MA, Hughes GR. Systemic lupus erythematosus. Lancet 2007;369:587–96.
2. Krupp LB, LaRocca NG, Muir J, Steinberg AD. A study of fatigue in systemic lupus erythematosus. J Rheumatol 1990;17:1450–2.
3. Balsamo S, da Mota LM, de Carvalho JF, Nascimento Dda C, Tibana RA, de Santana FS, et al. Low dynamic muscle strength and its associations with fatigue, functional performance, and quality of life in premenopausal patients with systemic lupus erythematosus and low disease activity: a case-control study. BMC Musculoskelet Disord 2013;14:263–9.
4. Williams AE, Crofts G, Teh LS. 'Focus on feet': the effects of systemic lupus erythematosus: a narrative review of the literature. Lupus 2013;22:1017–23.
5. Iagnocco A, Ceccarelli F, Rizzo C, Truglia S, Massaro L, Spinelli FR, et al. Ultrasound evaluation of hand, wrist and foot joint synovitis in systemic lupus erythematosus. Rheumatology (Oxford) 2014;53:465–72.
6. Otter SJ, Kumar S, Gow P, Dalbeth N, Corkill M, Rohan M, et al. Patterns of foot complaints in systemic lupus erythematosus: a cross sectional survey. J Foot Ankle Res 2016;9:10–17.
7. Cherry L, Alcacer-Pitarch B, Hopkinson N, Teh LS, Vital EM, Edwards CJ, et al. The prevalence of self-reported lower limb and foot health problems experienced by participants with systemic lupus erythematosus: results of a UK national survey. Lupus 2017;26:410–6.
8. Mukherjee S, Cherry L, Zarroug J, Culliford D, Bowen C, Arden N, et al. A pilot investigation of the prevalence of US-detectable forefoot joint pathology and reported foot-related disability in participants with systemic lupus erythematosus. J Foot Ankle Res 2016;9:27–33.
9. Petri M, Orbai AM, Alarcón GS, Gordon C, Merrill JT, Fortin PR, et al. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. Arthritis Rheum 2012;64:2677–86.
10. Deandrade JR, Casagrande PA. A seven-day variability study of 499 patients with peripheral rheumatoid arthritis. Arthritis Rheum 1965;8:302–34.
11. Gladman DD, Ibanez D, Urowitz MB. Systemic lupus erythematosus disease activity index 2000. J Rheumatol 2002;29:288–91.
12. Wang CY, Olson SL, Protas EJ. Test-retest strength reliability: hand-held dynamometry in community-dwelling elderly fallers. Arch Phys Med Rehabil 2002;83:811–5.
13. Hopson MM, McPoil TG, Cornwall MW. Motion of the first metatarsophalangeal joint: reliability and validity of four measurement techniques. J Am Podiatr Med Assoc 1995;85:198–204.
14. Menadue C, Raymond J, Kilbreath SL, Refshauge KM, Adams R. Reliability of two goniometric methods of measuring active inversion and eversion range of motion at the ankle. BMC Musculoskelet Disord 2006;7:60–7.
15. Bennell KL, Talbot RC, Wajswelner H, Techovanich W, Kelly DH, Hall AJ. Intra-rater and inter-rater reliability of a weight-bearing lunge measure of ankle dorsiflexion. Aust J Physiother 1998;44:175–80.
16. Redmond AC, Crosbie J, Ouvrier RA. Development and validation of a novel rating system for scoring standing foot posture: the Foot Posture Index. Clin Biomech 2006;21:89–98.
17. Aquino MR, Avelar BS, Silva PL, Ocarino JM, Resende RA. Reliability of Foot Posture Index individual and total scores for adults and older adults. Musculoskelet Sci Pract 2018;36:92–5.
18. Menz HB, Lord SR. The contribution of foot problems to mobility impairment and falls in community-dwelling older people. J Am Geriatr Soc 2001;49:1651–6.
19. Zammit GV, Menz HB, Munteanu SE. Reliability of the TekScan MatScan system for the measurement of plantar forces and pressures during barefoot level walking in healthy adults. J Foot Ankle Res 2010;3:11–9.
20. Bohannon RW. Comfortable and maximum walking speed of adults aged 20–79 years: reference values and determinants. Age Ageing 1997;26:15–9.
21. Feng Y, Schlosser FJ, Sumpio BE. The Semmes Weinstein monofilament examination as a screening tool for diabetic peripheral neuropathy. J Vasc Surg 2009;50:675–82.
22. Young MJ, Every N, Boulton AJ. A comparison of the neurothesiometer and biothesiometer for measuring vibration perception in diabetic patients. Diabetes Res Clin Pract 1993;20:129–31.
23. Sacks D, Bakal CW, Beatty PT, Becker GJ, Cardella JF, Raabe RD, et al. Position statement on the use of the ankle-brachial index in the evaluation of patients with peripheral vascular disease: a consensus statement developed by the standards division of the society of cardiovascular & interventional radiology. J Vasc Interv Radiol 2002;13:353.
24. Chatterton BD, Muller S, Thomas MJ, Menz HB, Rome K, Roddy E. Inter and intra-rater repeatability of the scoring of foot pain drawings. J Foot Ankle Res 2013;6:44–50.
25. Garrow AP, Papageorgiou AC, Silman AJ, Thomas E, Jayson MI, Macfarlane GJ. Development and validation of a questionnaire to assess disabling foot pain. Pain 2000;85:107–13.

26. McNair PJ, Prapavessis H, Collier J, Bassett S, Bryant A, Larmer P. The lower-limb tasks questionnaire: an assessment of validity, reliability, responsiveness, and minimal important differences. Arch Phys Med Rehabil 2007;88:993–1001.
27. Morpeth T, Brenton-Rule A, Carroll M, Frecklington M, Rome K. Fear of falling and foot pain, impairment and disability in rheumatoid arthritis: a case-control study. Clin Rheumatol 2016;35:887–91.
28. Stewart S, Pearson J, Rome K, Dalbeth N, Vandal AC. Analysis of data collected from right and left limbs: accounting for dependence and improving statistical efficiency in musculoskeletal research. Gait Posture 2018;59:182–7.
29. Tench C, Bentley D, Vleck V, McCurdie I, White P, D'Cruz D. Aerobic fitness, fatigue, and physical disability in systemic lupus erythematosus. J Rheumatol 2002;29:474–81.
30. Stockton KA, Kandiah DA, Paratz JD, Bennell KL. Fatigue, muscle strength and vitamin D status in women with systemic lupus erythematosus compared with healthy controls. Lupus 2012;21:271–8.
31. Brockett CL, Chapman GJ. Biomechanics of the ankle. Orthop Trauma 2016;30:232–8.
32. Armstrong DG, Peters EJG, Athanasiou KA, Lavery LA. Is there a critical level of plantar foot pressure to identify patients at risk for neuropathic foot ulceration? J Foot Ankle Surg 1998;37:303–7.
33. Van der Leeden M, Steultjens M, Dekker JH, Prins AP, Dekker J. Forefoot joint damage, pain and disability in rheumatoid arthritis patients with foot complaints: the role of plantar pressure and gait characteristics. Rheumatology (Oxford) 2006;45:465–9.
34. Stewart S, Morpeth T, Dalbeth N, Vandal AC, Carroll M, Davidtz L, et al. Foot-related pain and disability and spatiotemporal parameters of gait during self-selected and fast walking speeds in people with gout: a two-arm cross sectional study. Gait Posture 2015;44:18–22.
35. Turner DE, Woodburn J. Characterising the clinical and biomechanical features of severely deformed feet in rheumatoid arthritis. Gait Posture 2008;28:574–80.
36. Reilly PA, Evison G, McHugh NJ, Maddison PJ. Arthropathy of hands and feet in systemic lupus erythematosus. J Rheumatol 1990;17:777–84.
37. Morales-Lozano R, Martinez-Barrio J, Gonzalez-Fernandez ML, Lopez-Longo FJ, Ovalles-Bonilla JG, Valor L, et al. The feet in systemic lupus erythematosus; are we underestimating their involvement and functional impact? Clin Exp Rheumatol 2016; 34:609–17.
38. Pipili C, Sfritzeri A, Cholongitas E. Deforming arthropathy in systemic lupus erythematosus. Eur J Int Med 2008;19:482–7.
39. Omdal R, Mellgren SI, Husby G, Salvesen R, Heriksen OA, Torbergsen T. A controlled study of peripheral neuropathy in systemic lupus erythematosus. Acta Neurol Scand 1993;88:41–6.
40. Tseng MT, Hsieh SC, Shun CT, Lee KL, Pan CL, Lin WM, et al. Skin denervation and cutaneous vasculitis in systemic lupus erythematosus. Brain 2006;129:977–85.
41. Hassan AA, Habib HM, Eissa AA. Peripheral arterial disease in patients with systemic lupus erythematosus: a prospective controlled study. Int J Rheum Dis 2013;16:319–24.
42. June RR, Scalzi LV. Peripheral vascular disease in systemic lupus patients. J Clin Rheumatol 2013;19:367–72.
43. Erdozain JG, Villar I, Nieto J, Ruiz-Irastorza G. Peripheral arterial disease in systemic lupus erythematosus: prevalence and risk factors. J Rheumatol 2014;41:310–7.
44. Heimovski FE, Simioni JA, Skare TL. Systemic lupus erythematosus and Raynaud's phenomenon. An Bras Dermatol 2015;90:837–40.
45. Rome K, Erikson K, Ng A, Gow PJ, Sahid H, Williams AE. A new podiatry service for patients with arthritis. N Z Med J 2013;126:70–7.
46. Stewart S, Keys M, Brenton-Rule A, Aiyer A, Dalbeth N, Rome K. Characteristics of footwear worn by people with systemic lupus erythematosus: a comparison with age- and sex-matched healthy controls: a pilot study. J Foot Ankle Res 2018;11:38–43.

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Cardiovascular Morbidity and Mortality in Primary Sjögren's Syndrome: A Systematic Review and Meta-Analysis

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Objective. Patients with immune-mediated inflammatory diseases such as rheumatoid arthritis or systemic lupus erythematosus are at increased risk of cardiovascular disease. However, the cardiovascular risk of patients with primary Sjögren's syndrome (SS) remains poorly studied. We aimed to investigate the association between primary SS and cardiovascular morbidity and mortality.

Methods. We performed a systematic review of articles in Medline and the Cochrane Library and recent abstracts from US and European meetings, searching for reports of randomized controlled studies of cardiovascular morbidity and cardiovascular mortality in primary SS. The relative risk (RR) values for cardiovascular morbidity and mortality associated with primary SS were collected and pooled in a meta-analysis with a random-effects model by using Review Manager (Cochrane collaboration).

Results. The literature search revealed 484 articles and abstracts of interest; 14 studies (67,124 patients with primary SS) were included in the meta-analysis. With primary SS versus control populations, the risk was significantly increased for coronary morbidity (RR 1.34 [95% confidence interval (95% CI) 1.06–1.38]; $P = 0.01$), cerebrovascular morbidity (RR 1.46 [95% CI 1.43–1.49]; $P < 0.00001$), heart failure rate (odds ratio 2.54 [95% CI 1.30–4.97]; $P < 0.007$), and thromboembolic morbidity (RR 1.78 [95% CI 1.41–2.25]; $P < 0.00001$), with no statistically significant increased risk of cardiovascular mortality (RR 1.48 [95% CI 0.77–2.85]; $P = 0.24$).

Conclusion. This meta-analysis demonstrates that primary SS is associated with increased cardiovascular morbidity, which suggests that these patients should be screened for cardiovascular comorbidities and considered for preventive interventions, in a multidisciplinary approach with cardiologists.

INTRODUCTION

Primary Sjögren's syndrome (SS) is a chronic autoimmune disease with a prevalence of 6.8 per 10,000. The peak frequency of the disease is approximately age 50 years and it predominantly affects women, with a 9:1 female:male ratio. If SS is associated with another systemic disease, it can also be labeled as secondary (1). Primary SS is characterized by lymphocytic infiltration of the exocrine glands (mainly salivary and lacrimal) responsible for oral and eye dryness and by B-cell hyperactivity (2). Patients with chronic autoimmune diseases such as rheumatoid arthritis (RA) and systemic lupus erythematosus are at increased risk of cardiovascular disease, largely because of the systemic inflammation (3,4). In RA, the cardiovascular disease is the main cause of death. Publications on primary SS show different estimations of the incidence of cardiovascular complications. This heterogeneity of data led us to conduct a systematic review of this topic. We performed a meta-analysis of all studies that estimated cardiovascular events with primary SS as compared with controls.

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SIGNIFICANCE & INNOVATIONS

- Patients with primary Sjögren's syndrome are at increased risk of cardiovascular morbidity as compared with the general population.
- Studies of cardiovascular morbidity and mortality in patients with primary Sjögren's syndrome are limited and results are conflicting; this meta-analysis improves the literature data.
- The study adds additional data to a recent meta-analysis.

PATIENTS AND METHODS

Search strategy and selection criteria. Studies were included in the systematic review if all of the following criteria were met: 1) it was a cross-sectional, prospective-cohort, retrospective-cohort, or case–control study accounting for the number of cardiovascular events (myocardial infarction, cerebrovascular events, thromboembolic events, heart failure, or cardiovascular mortality); 2) the patients who were the index cases were adults ages ≥18 years; 3) the primary SS diagnosis was based on the 1993 European Community Study Group or American-European Consensus Group (AECG) criteria for primary SS or the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code 710.2 or ICD-10-CM code M35.0; 4) there was a control group of healthy individuals; and 5) the results of selected studies were published in English.

Patients with secondary SS or another immune-mediated inflammatory disease (IMID) were excluded. Controls did not have any IMID. Potentially eligible studies were identified by a literature search of articles published up to March 2018 in Medline (National Library of Medicine) with the following medical subject heading (MeSH) terms: ("Sjögren's syndrome" OR "Sjögren's syndrome/complications") AND ("cardiovascular diseases/complications" OR "cardiovascular diseases/mortality" OR "myocardial ischemia" OR "heart failure" OR "stroke").

Electronic abstract databases of the annual scientific meetings of the European League Against Rheumatism and the American College of Rheumatology were also screened. Finally, the references of selected articles were screened to search for additional studies. Studies were reviewed by 2 independent readers (AB, JM). Disagreements were resolved by consensus.

Data extraction. Data were extracted by one reader (AB) from the selected studies and included the first author's name, publication date, country, number of patients with primary SS, disease duration, follow-up duration, classification criteria used, autoantibody status, type of control group, number of controls, percentage of women, and mean age (Table 1). Possible confounding factors extracted included the percentage of comorbidities, such as diabetes mellitus, hypertension, smoking, obesity, hyperlipidemia, and steroid use (Table 2).

Data analysis. From information provided by observational studies, we estimated the risk of cardiovascular disease (myocardial infarction, cerebrovascular events, thromboembolic events, heart failure, or cardiovascular mortality) for patients with primary SS versus the control group. Relative risks (RRs), odds ratios (ORs), and 95% confidence intervals (95% CIs) were calculated by using a 0.05 alpha risk.

The Mantel-Haenszel procedure was used to evaluate the association between cardiovascular events and primary SS. This method provided a common RR or OR estimate and 95% CIs in forest plots, highlighting the population-wide effect of primary SS status on the risk of cardiovascular disease. Statistical heterogeneity of the samples was assessed by the Q test (chi-square), with a significance level of 0.05, and was reported with the I^2 statistic (high values indicating high heterogeneity). Data analyses involved using Revman software, version 5.3 (5). The quality of observational studies was evaluated by the Cochrane risk of bias tool for nonrandomized studies of interventions (Table 2). Details are provided in Supplementary Table 1, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23821/abstract.

RESULTS

Our search strategy yielded 484 studies; 468 studies were excluded because they had the wrong population (i.e., not about primary SS [n = 85], not adults [n = 4], or with a control group composed of individuals diagnosed for an autoimmune disease [n =1]), wrong outcome (not about cardiovascular disease [n = 139]), or wrong type of study (case reports [n = 207] or editorial [n = 12]), were duplicates (n = 18), or were not published in English (n = 2). The flowchart is shown in Figure 1. Finally, 28 publications (including 1 abstract) were eligible for inclusion in the review; 14 publications had sufficient data to be included in the meta-analysis. Within these 14 publications (11 retrospective and 3 prospective), 9 were from European countries, 2 from the US and Canada, and 3 from Taiwan. Five studies focused on coronary morbidity, 4 on cerebrovascular morbidity, 3 on heart failure rate, 2 on thromboembolic morbidity, and 2 on cardiovascular mortality.

Selected studies included mostly women (approximately 90% for patients with primary SS and 74.5% for controls [6–12]). The mean ± SD age of patients with primary SS was 55.5 ± 13.5 years (8–10), with a mean age of 75 years for age at death (13). The mean age of controls was 54.5 ± 12.4 years (8–10). Follow-up duration was from 3.6 to 44 years (6,7,10–12,14–17). The disease duration from diagnosis at inclusion, reported in 4 studies (8,9,13,14), was approximately 7 years. Classification

Table 1. Characteristics of studies selected for the meta-analysis*

Reference	Country	Type of event	Primary SS patients, no.	Classification criteria (%)	SSA/SSB status, %	Disease duration, years	Follow-up, years	Control group	Controls, no.	Women, %	Age, mean
Theander et al, 2004 (13)	Sweden	Mortality	484	AECG criteria: 55; Copenhagen criteria or 1993 European criteria: 45	56	8	7	General population of Malmö matched for sex, age, and calendar period of observation	NR	pSS: 91; controls: NR	pSS: 75 (at death); controls: NR
Skopouli et al, 2000 (14)	Greece	Mortality	261	1993 European criteria: 100	56	9.5	3.6	General Greek population, adjusting for age and sex	NR	pSS: 96; controls: NR	pSS: NR; controls: NR
Ramagopalan et al, 2013 (6)	UK	Cerebrovascular morbidity	17,741	NR	NR	NR	12	Reference cohort constructed by identifying the first admission for each individual with various other, mainly minor, medical and surgical, conditions from data set of English National Hospital Episode Statistics	17,741	SS: 89; controls: 48	SS: NR; controls: NR
Vassiliou et al, 2008 (8)	Greece	Heart failure (echocardiographic abnormalities)	107	AECG criteria: 100	NR	6	Irrelevant	Healthy controls, matched for age and sex, visitors to the hospital	112	pSS: 96.2; controls: 96.4	pSS: 56.5 ± 12.5; controls: 55.4 ± 12.2
Bartoloni et al, 2015 (9)	Italy	Myocardial infarction, cerebrovascular morbidity, heart failure	1,343 (788 for comparison)	1993 European Community Study Group diagnostic and/or the revised classification criteria for pSS proposed in 2002 by the AECG	68	5 ± 6	NR	Age-matched healthy women from an Italian registry	4,774	pSS: 100; controls: 100	pSS: 57 ± 14; controls: 55 ± 11
Chiang et al, 2013 (10)	Taiwan	Myocardial infarction	5,025	AECG criteria: 100	NR	NR	3.7	Controls matched by age, sex, date of enrollment, and presence of comorbid disorders without any record of autoimmune diseases from Taiwan's National Health Insurance	5,025	SS: 87; controls: 87	SS: 53.0 ± 14; controls: 53.2 ± 14.1
Chiang et al, 2014 (11)	Taiwan	Cerebrovascular morbidity	4,276	AECG criteria: 100	NR	NR	3.7	Controls matched by age, sex, date of enrollment, and presence of comorbid disorders without any record of autoimmune diseases from Taiwan's National Health Insurance	42,760	SS: 88.4; controls: 88.4	SS: 51.6 ± 13.7; controls: 51.6 ± 13.7

(Continued)

Table 1. (*Cont'd*)

Reference	Country	Type of event	Primary SS patients, no.	Classification criteria (%)	SSA/SSB status, %	Disease duration, years	Follow-up, years	Control group	Controls, no.	Women, %	Age, mean
Zöller et al, 2012 (15)	Sweden	Cerebrovascular morbidity	1,300	ICD-9-CM code 710.2, ICD 10-CM code M35.0	NR	NR	21	Total population of Sweden (adjusted for individual variables, including age and sex, time period, and comorbidity) from a database	NR	pSS: 88	pSS: NR; controls: NR
Zöller et al, 2012 (16)	Sweden	Myocardial infarction	1,420	ICD-9-CM code 710.2, ICD 10-CM code M35.0	NR	NR	44	Total population of Sweden (adjusted for individual variables, including age and sex, time period, and comorbidity) from a database	NR	pSS: 90.4	pSS: NR controls: NR
Zöller et al, 2012 (17)	Sweden	Thromboembolism morbidity	3,410	ICD-9-CM code 710.2, ICD 10-CM code M35.0	NR	NR	44	Total population of Sweden (adjusted for individual variables, including age and sex, time period, and comorbidity) from a database	NR	pSS: 89.88	PSS: NR; controls: NR
Ramagopalan et al, 2011 (7)	UK	Venous thromboembolism	12,680	ICD-9-CM code 710.2, ICD 10-CM code M35.0	NR	NR	9	Reference cohort constructed by identifying the first admission for each individual with various other, mainly minor, medical and surgical conditions	NR	pSS: 89; controls: NR	pSS: NR; controls: NR
Yurkovich et al, 2014 (18)	Canada	Myocardial infarction, cerebrovascular morbidity	Myocardial infarction cohort: n = 1,176; cerebro-vascular cohort: n = 1,195	ICD-9-CM code 710.2, ICD 10-CM code M35.0	NR	NR	NR	Age-, sex- and entry time–matched cohort from databases covering entire population of British Columbia	Myocardial infarction cohort: 11,879; erebro-vascular morbidity cohort: 11,983	pSS: NR;controls: NR	pSS: NR; controls: NR
Luni et al, 2016 (19)	US	Myocardial infarction	13,086	ICD-9-CM code 710.2	NR	NR	NR	Controls matched 1:4 for age, sex and hospital region from a national database	52,448	pSS: NR;controls: NR	pSS: NR; controls: NR
Wu et al, 2018 (12)	Taiwan	Coronary heart disease	4,175	ICD-9-CM code 710.2	NR	NR	11	Controls individually matched with pSS patients at a 4:1 ratio based on sex and age	16,700	pSS: 75.40; ontrols: 75.40	pSS: NR; controls: NR

* SS = Sjögren's syndrome; AECG = American-European Consensus Group; NR = not reported; pSS = primary SS; ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification; ICD-10-CM = International Classification of Diseases, Tenth Revision, Clinical Modification.

Table 2. Potential confounding factors and assessment risk of bias of studies selected*

Author, year (ref.)	Cardiovascular risk factors	Corticosteroids use	Overall risk of bias
Theander et al, 2004 (13)	Primary SS: NR; controls: NR	Primary SS: NR; controls: NR	Serious
Skopouli et al, 2000 (14)	Primary SS: NR; controls: NR	Primary SS: NR; controls: NR	Serious
Ramagopalan et al, 2013 (6)	Primary SS: NR; controls: NR	Primary SS: NR; controls: NR	Serious
Vassiliou et al, 2008 (8)	Primary SS: NR; controls: NR	Primary SS: NR; controls: NR	Serious
Bartoloni et al, 2015 (9)	Hypertension: primary SS (32%), comparator (28%), $P = 0.021$; hypercholesterolemia: primary SS (30%), comparator (23%), $P < 0.001$; obesity: primary SS (11%), comparator (21%), $P < 0.001$; smoking: primary SS (13%), comparator (23%), $P < 0.001$; diabetes mellitus: primary SS (4%), comparator (7%), $P = 0.001$	Primary SS: NR; controls: NR	Moderate
Ramagopalan et al, 2011 (7)	Primary SS: NR; controls: NR	Primary SS: NR; controls: NR	Serious
Chiang et al, 2013 (10)	Hypertension: primary SS (1,614; 32.1%); controls (1,633; 32.5%), NS; diabetes mellitus: primary SS (1,050; 20.9%); controls (1,056; 21.0%), NS; hyperlipidemia: primary SS (1,378; 27.4%); controls (1,421; 28.3%), NS	Primary SS: NR; controls: NR	Low
Chiang et al, 2014 (11)	Hypertension: pSS (1,155; 27.0%), controls (11,561; 27.0%), $P = 0.985$; diabetes mellitus: pSS (809; 18.9%), controls (8,088; 18.9%), $P > 0.999$; hyperlipidemia: pSS (966; 22.6%), controls (9,663; 22.6%), $P = 0.999$	Primary SS: NR; controls: NR	Low
Zöller et al, 2012 (15)	Primary SS: NR; controls: NR	Primary SS: NR; controls: NR	Moderate
Zöller et al, 2012 (16)	Primary SS: NR; controls: NR	Primary SS: NR; controls: NR	Moderate
Zöller et al, 2012 (17)	Primary SS: NR; controls: NR	Primary SS: NR; controls: NR	Moderate
Yurkovich et al, 2014 (18)	Primary SS: NR; controls: NR	Primary SS: NR; controls: NR	Moderate
Luni et al, 2016 (19)	Primary SS: NR; controls: NR	Primary SS: NR; controls: NR	Moderate
Wu et al, 2018 (12)	Hypertension: primary SS (955; 22.87%); controls (3,286; 19.68%); diabetes mellitus: primary SS (509; 12.19%); controls (1,535; 9.19%); hyperlipidemia: primary SS (733; 17.56%); controls (2,122; 12.71%)	Primary SS (464; 11.11%); controls (371; 2.22%)	Moderate

* SS = Sjögren's syndrome; NR = not reported; NS = not significant.

criteria for primary SS patients were reported in 13 publications; the ICD code was used in 7 studies (7,12,15–19), AECG criteria in 3 studies (8,10,11), 1993 European criteria in 1 study (14), and 2 studies used AECG criteria and 1993 European criteria (9,13). The autoantibody status of patients with primary SS was reported in 3 studies (9,13,14). Data on coexisting cardiovascular risk factors and treatments, such as corticosteroids, were reported in 4 studies (Table 2).

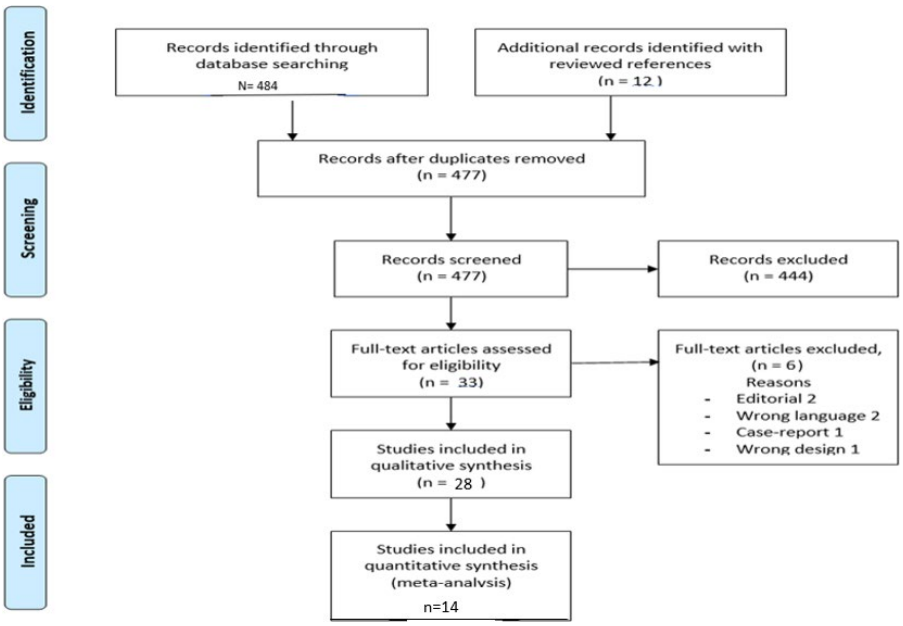

Figure 1. Flow chart of literature selection process. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/acr.23821/abstract.

RR of cerebrovascular events. Four articles (6,10,15,18) compared the number of cerebrovascular events in patients with primary SS to that in the general population. The total number of patients with primary SS was 25,242, and the number of cerebrovascular events in this population was 605. Among the 570,183 patients with nonprimary SS, the number of cerebrovascular events

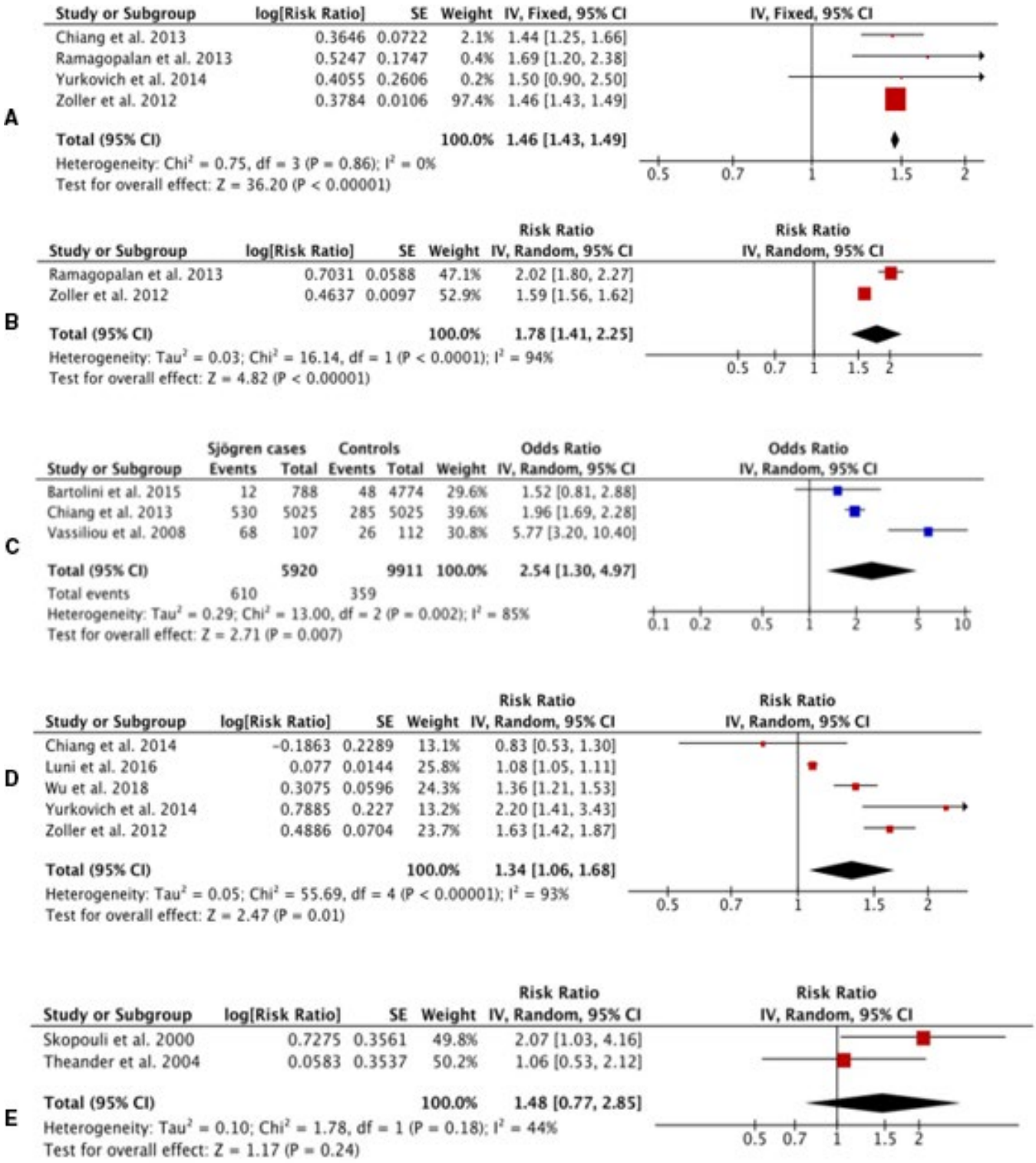

Figure 2. Risk ratios (RRs) with 95% confidence intervals (95% CIs) for cerebrovascular events (**A**), thromboembolic events (**B**), heart failure rate (**C**), coronary morbidity (**D**), and cardiovascular mortality (**E**). The pooled RRs with 95% CIs for overall analysis in the total population were estimated by the Mantel-Haenszel method (diamond).

was 11,367. The risk of a cerebrovascular event was increased for patients with primary SS versus the general population (RR 1.46 [95% CI 1.43–1.49]; $P < 0.00001$; $I^2 = 0\%$) (Figure 2A).

RR of thromboembolic events. Two articles (6,7) compared the number of thromboembolic events in patients with primary SS to that in the general population. The total of patients with primary SS was 16,090, and the number of thromboembolic events in this population was 100. Among the 548,218 patients with nonprimary SS, the number of thromboembolic events was 15,607. The risk of a thromboembolic event was increased for patients with primary SS versus the general population (RR 1.78 [95% CI 1.41–2.25]; $P < 0.00001$; $I^2 = 94\%$) (Figure 2B).

Odds of heart failure. Three articles (8–10) compared the rate of heart failure in patients with primary SS to that in the general population. The total number of patients with primary SS was 5,920, and the number of heart failures in this population was 609. Among the 9,911 patients with nonprimary SS, the rate of heart failure was 358. The likelihood of heart failure was increased for patients with primary SS versus the general population (OR 2.54 [95% CI 1.30–4.97]; $P < 0.007$; $I^2 = 85\%$) (Figure 2C).

RR of coronary morbidity. Five articles (11,12,16,18,19) compared the rate of coronary events in patients with primary SS to that in the general population. The total number of patients with primary SS was 24,133, and the number of coronary events in this population was 7,799. Among the 460,266 patients with nonprimary SS, the number of coronary events was 84,772. The risk of coronary events was increased for patients with primary SS versus the general population (RR 1.34 [95% CI 1.06–1.68]; $P = 0.01$; $I^2 = 95\%$) (Figure 2D).

RR of cardiovascular mortality. Two cohort studies (13,14) compared the cardiac-related death in primary SS patients to that in the general population. The total number of patients with primary SS was 745, and the rate of cardiac-related deaths was 25. Cardiovascular mortality was not significantly increased for patients with primary SS (RR 1.48 [95% CI 0.77–2.85]; $P = 0.24$; $I^2 = 44\%$) (Figure 2E).

DISCUSSION

In the present meta-analysis, we reported a 30% to 60% increased risk of coronary and cerebrovascular morbidity. These results are consistent with the study of Wu et al (12) that found a risk of coronary heart disease increased to 1.52 among patients with primary SS, after excluding all the patients with complications from diabetes mellitus, hypertension, hyperlipidemia, or chronic obstructive pulmonary disease and those who used antihyperglycemic and antihypertensive drugs, statins, and aspirin, suggesting that primary SS may itself be an independent risk factor for coronary heart disease. Similarly, Zöller et al (15) found a risk of ischemic stroke ≥2 during the first year after hospitalization, whereas Ramagopalan et al (6) found a risk of subarachnoid hemorrhage after hospital admission for primary SS increased to 1.69. Our study also shows an 80% increased risk of thromboembolic morbidity, which is consistent with the study of Ramagopalan et al (7) that found an elevated risk of venous thromboembolism after hospital admission >2 in primary SS patients. In our meta-analysis, we found a doubled risk of heart failure rate for patients with primary SS versus the general population. In their retrospective cohort of 1,343 patients, Bartoloni et al (9) found that heart failure represented the most common overt cardiovascular manifestation after cerebrovascular events. Risk of cardiovascular mortality was not significantly increased in our study. The studies of Theander et al (13) and Skopouli et al (14) did not detect any increased cardiovascular mortality either. For the authors, possible explanations include the lower frequencies of smoking and steroid use in patients with primary SS compared with patients with RA or systemic lupus erythematosus, in whom an increased risk of cardiovascular mortality is demonstrated.

A recent systematic review and meta-analysis also explored the risk of cardiovascular and cerebrovascular disease in patients with primary SS (20). As in our study, Yong et al found a significantly increased risk of cardiovascular disease or cerebrovascular events in patients with primary SS as compared with controls. However, subgroup analysis showed no difference in risk of cerebrovascular events, whereas our study showed a significantly increased risk of all cardiovascular events except cardiovascular mortality. Regardless, there are several differences between the 2 meta-analyses. The first is that we studied various aspects of cardiovascular morbidity and did not limit the research to cerebrovascular and coronary events. Another difference is the choice of included studies. Yong et al did not include abstracts of the last international meetings (18), but they included studies in which the outcome was not exclusively cardiovascular events. Indeed, 1 of the studies focused on cardiovascular risk factors and not cardiovascular events (21), and 2 other studies examined the risk of viral hepatitis and gastroesophageal reflux disease in patients with primary SS (22,23). Cardiovascular events were reported only in the initial characteristics. In addition, in our subgroup analysis of cerebrovascular events, we did not include the studies by Pasoto et al and Bartoloni et al (9,24) because the main outcome was not cardiovascular events. However, these 2 studies also showed an increased risk of ischemic stroke, although it was not significant in the study by Bartoloni et al.

Like other IMIDs, primary SS may lead to increased cardiovascular risk because of chronic inflammation. RA clearly increases cardiovascular risk, ischemic heart disease in particular (25), by causing atherosclerotic plaques. Some studies have also shown an increased prevalence of atherosclerosis in patients with primary SS measured by different methods: endothelial dysfunction (26),

increased carotid intima-media thickening (27), abnormal ankle brachial index (28), and pulse wave velocity (29). Rachapalli et al (28) demonstrated no significant reduction in ankle-brachial index, a simple method to identify subclinical atherosclerosis, in patients with primary SS, except for those with a disease duration >10 years. Two studies (27,30) also showed disease duration that was longer for patients with than without increased intima-media thickening. Similarly, Chiang et al (11) found no difference in the risk of acute myocardial infarction between patients with primary SS and age-, sex-, and comorbidity-matched controls. The authors explained this difference compared to other studies by disease duration. Indeed, they examined newly diagnosed patients with primary SS and followed them for up to 7 years.

In studies showing cardiovascular risk factors, patients with primary SS showed a significantly higher prevalence of several risk factors such as hypertension and hyperlipidemia, which may also play a role in atherosclerosis in primary SS (9,11). Other factors associated with subclinical atherosclerosis in patients with primary SS include anti-SSA/SSB antibodies. Indeed Bartoloni et al (9) showed that circulating anti-SSA/Ro and anti-SSB/La antibodies were more frequent in patients with primary SS with cardiovascular events. These antibodies are frequently present in primary SS with systemic involvement. Bartoloni et al reported that the main immunologic features in patients reporting visceral systemic involvement were antinuclear antibodies and anti-SSA/Ro positivity. Moreover, the authors also showed that primary SS patients with ≥1 cardiovascular event had an increased frequency of visceral involvement, in particular in the lung and central nervous system, and more frequently received glucocorticoids and immunosuppressive therapies. The systemic forms requiring aggressive therapies are more inflammatory and are thus associated with increased cardiovascular risk. However, treatment with corticosteroids may affect the risk of cardiovascular events itself. In addition, Pasoto et al (24) explored thrombotic and nonthrombotic manifestations of antiphospholipid syndrome in patients with primary SS and found that all patients with primary SS with antiphospholipid syndrome were positive for anti-SSA/Ro antibodies.

The main limitation of our study is the high heterogeneity among the studies of cardiovascular morbidity in patients with primary SS. One explanation could be that in some publications, classifications used by the authors (ICD-9-CM and ICD-10-CM) do not provide information on the type of SS (primary or secondary). However, most of the studies used the 1993 European or AECG criteria. The impact of cardiovascular risk factors, such as smoking, hypertension, hyperlipidemia, diabetes mellitus, or even use of corticosteroids, was not assessed because of missing data. These factors were not reported in all the studies and may suggest bias (31–39).

This meta-analysis confirms that patients with primary SS show an increased risk of cardiovascular disease as compared with the general population. Mechanisms underlying the increased risk of cardiovascular events in primary SS are not exactly elucidated: the respective weight of classical risk factors is not clearly determined. Prospective studies are needed to further study the association between cardiovascular events and primary SS by including the weight of corticosteroids and other cardiovascular risk factors. However, rheumatologists should be aware of this increased risk in order to propose screening for cardiovascular comorbidities and specific preventive interventions for patients with primary SS.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Morel had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Beltai, Combe, Morel.

Acquisition of data. Beltai.

Analysis and interpretation of data. Beltai, Barnetche, Daien, Lukas, Gaujoux-Viala, Combe, Morel.

REFERENCES

1. Qin B, Jiaqi W, Zaixing Y, Min Y, Ning M, Fenglou H, et al. Epidemiology of primary Sjögren's syndrome: a systematic review and meta-analysis. Ann Rheum Dis 2015;74:1983–9.
2. Mavragani CP, Moutsopoulos HM. Sjögren syndrome. CMAJ 2014;186:E579–86.
3. Crowson CS, Liao KP, Davis JM, Solomon DH, Matteson EL, Knutson KL, et al. Rheumatoid arthritis and cardiovascular disease. Am Heart J 2013;166:622–8.
4. Barbhaiya M, Solomon DH. Rheumatoid arthritis and cardiovascular disease: an update on treatment issues. Curr Opin Rheumatol 2013;25:317–24.
5. Review Manager (RevMan) [computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration; 2014.
6. Ramagopalan SV, Pakpoor J, Seminog O, Goldacre R, Graham L, Goldacre MJ. Risk of subarachnoid haemorrhage in people admitted to hospital with selected immune-mediated diseases: record-linkage studies. BMC Neurol 2013;13:176.
7. Ramagopalan SV, Wotton CJ, Handel AE, Yeates D, Goldacre MJ. Risk of venous thromboembolism in people admitted to hospital with selected immune-mediated diseases: record-linkage study. BMC Med 2011;9:1.
8. Vassiliou VA, Moyssakis I, Boki KA, Moutsopoulos HM. Is the heart affected in primary Sjögren's syndrome? An echocardiographic study Clin Exp Rheumatol 2008;26:109–12.
9. Bartoloni E, Baldini C, Schillaci G, Quartuccio L, Priori R, Carubbi F, et al. Cardiovascular disease risk burden in primary Sjögren's syndrome: results of a population-based multicentre cohort study. J Intern Med 2015;278:185–92.

10. Chiang CH, Liu CJ, Chen PJ, Leu HB, Hsu CY, Huang PH, et al. Primary Sjögren's syndrome and the risk of acute myocardial infarction: a nationwide study. Acta Cardiol Sin 2013;29:124–31.
11. Chiang CH, Liu CJ, Chen PJ, Huang CC, Hsu CY, Chan WL, et al. Primary Sjögren's syndrome and risk of ischemic stroke: a nationwide study. Clin Rheumatol 2014;33:931–7.
12. Wu XF, Huang JY, Chiou JY, Chen HH, Wei JC, Dong LL. Increased risk of coronary heart disease among patients with primary Sjögren's syndrome: a nationwide population-based cohort study. Sci Rep 2018;8:2209.
13. Theander E, Manthorpe R, Jacobsson LT. Mortality and causes of death in primary Sjögren's syndrome: a prospective cohort study. Arthritis Rheum 2004;50:1262–9.
14. Skopouli FN, Dafni U, Ioannidis JP, Moutsopoulos HM. Clinical evolution, and morbidity and mortality of primary Sjögren's syndrome. Semin Arthritis Rheum 2000;29:296–304.
15. Zöller B, Li X, Sundquist J, Sundquist K. Risk of subsequent ischemic and hemorrhagic stroke in patients hospitalized for immune-mediated diseases: a nationwide follow-up study from Sweden. BMC Neurol 2012;12:41.
16. Zöller B, Li X, Sundquist J, Sundquist K. Risk of subsequent coronary heart disease in patients hospitalized for immune-mediated diseases: a nationwide follow-up study from Sweden. PLoS One 2012;7:e33442.
17. Zöller B, Li X, Sundquist J, Sundquist K. Risk of pulmonary embolism in patients with autoimmune disorders: a nationwide follow-up study from Sweden. Lancet 2012;379:244–9.
18. Yurkovich M, Sayre EC, Shojania K, Avina-Zubieta A. The risk of the myocardial infarction and cerebrovascular accident in patients with Sjögren's syndrome: a general population-based cohort study [abstract]. Ann Rheum Dis 2014;73:142–3.
19. Luni FK, Malik SA, Khan AR, Riaz H, Singh H, Federman D, et al. Risk of ischemic heart disease in patients with Sjögren's syndrome. Am J Med Sci 2017;354:395–8.
20. Yong WC, Sanguankeo A, Upala S. Association between primary Sjögren's syndrome, cardiovascular and cerebrovascular disease: a systematic review and meta-analysis. Clin Exp Rheumatol 2018;36 Suppl:190–7.
21. Pérez-De-Lis M, Akasbi M, Sisó A, Diez-Cascon P, Brito-Zerón P, Diaz-Lagares C, et al. Cardiovascular risk factors in primary Sjögren's syndrome: a case-control study in 624 patients. Lupus 2010;19: 941–8.
22. Yeh CC, Wang WC, Wu CS, Sung FC, Su CT, Shieh YH, et al. Association of Sjögrens syndrome in patients with chronic hepatitis virus infection: a population-based analysis. PLoS One 2016;11:e0161958.
23. Chang CS, Liao CH, Muo CH, Kao CH. Increased risk of concurrent gastroesophageal reflux disease among patients with Sjögren's syndrome: a nationwide population-based study. Eur J Intern Med 2016;31:73–8.
24. Pasoto SG, Chakkour HP, Natalino RR, Viana VS, Bueno C, Lianza AC, et al. Lupus anticoagulant: a marker for stroke and venous thrombosis in primary Sjögren's syndrome. Clin Rheumatol 2012;31:1331–8.
25. Gonzalez-Gay MA, Gonzalez-Juanatey C, Martin J. Rheumatoid arthritis: a disease associated with accelerated atherogenesis. Semin Arthritis Rheum 2005;35:8–17.
26. Akyel A, Tavil Y, Tufan A, Yayla C, Kaya A, Tezcan ME, et al. Atrial electromechanical delay and diastolic dysfunction in primary Sjögren syndrome. Clin Invest Med 2012;35:E303.
27. Vaudo G, Bocci EB, Shoenfeld Y, Schillaci G, Wu R, Del Papa N, et al. Precocious intima-media thickening in patients with primary Sjögren's syndrome. Arthritis Rheum 2005;52:3890–7.
28. Rachapalli SM, Kiely PD, Bourke BE. Prevalence of abnormal ankle brachial index in patients with primary Sjogren's syndrome. Clin Rheumatol 2009;28:587–90.
29. Sabio JM, Sánchez-Berná I, Martinez-Bordonado J, Vargas-Hitos JA, Navarrete-Navarrete N, Expósito Ruíz M, et al. Prevalence of and factors associated with increased arterial stiffness in patients with primary Sjögren's syndrome. Arthritis Care Res (Hoboken) 2015;67:554–62.
30. Zardi EM, Basta F, Afeltra A. Levels of vitamin D, disease activity and subclinical atherosclerosis in post-menopausal women with Sjögren's syndrome: does a link exist? Vivo 2016;30:721–5.
31. Vitali C, Bombardieri S, Moutsopoulos HM, Balestrieri G, Bencivelli W, Bernstein RM, et al. Preliminary criteria for the classification of Sjögren's syndrome: results of a prospective concerted action supported by the European Community. Arthritis Rheum 1993;36:340–7.
32. Vitali C, Bombardieri S, Jonsson R, Moutsopoulos HM, Alexander EL, Carsons SE, et al, for the European Study Group on Classification Criteria for Sjögren's Syndrome. Classification criteria for Sjogren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. Ann Rheum Dis 2002;61:554–8.
33. Rúa-Figueroa I, Fernández Castro M, Andreu JL, Sanchez-Piedra C, Martínez-Taboada V, Olivé A, et al. Comorbidities in patients with primary Sjögren's syndrome and systemic lupus erythematosus: a comparative registries-based study. Arthritis Care Res (Hoboken) 2017;69:38–45.
34. Juarez M, Toms TE, de Pablo P, Mitchell S, Bowman S, Nightingale P, et al. Cardiovascular risk factors in women with primary Sjögren's syndrome: United Kingdom Primary Sjögren's Syndrome Registry results. Arthritis Care Res (Hoboken) 2014;66:757–64.
35. Shoenfeld Y, Gerli R, Doria A, Matsuura E, Cerinic MM, Ronda N, et al. Accelerated atherosclerosis in autoimmune rheumatic diseases. Circulation 2005;112:3337–47.
36. Ahmad Y, Bruce IN. Subclinical atherosclerosis in systemic lupus erythematosus. J Rheumatol 2004;31:841–3.
37. Shoenfeld Y, Wu R, Dearing LD, Matsuura E. Are anti-oxidized low-density lipoprotein antibodies pathogenic or protective? Circulation 2004;110:2552–8.
38. Selzer F, Sutton-Tyrrell K, Fitzgerald SG, Pratt JE, Tracy RP, Kuller LH, et al. Comparison of risk factors for vascular disease in the carotid artery and aorta in women with systemic lupus erythematosus. Arthritis Rheum 2004;50:151–9.
39. Pirildar T, Tikiz C, Ozkaya S, Tarhan S, Utük O, Tikiz H, et al. Endothelial dysfunction in patients with primary Sjogren's syndrome. Rheumatol Int 2005;25:536–9.

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Ten Years of Interventional Research in Systemic Sclerosis: A Systematic Mapping of Trial Registries

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Objective. To provide a comprehensive overview of interventional clinical trials registered in international databases and planned and conducted within the last 10 years in patients with systemic sclerosis (SSc).

Methods. We searched the International Clinical Trials Registry Platform for all records on interventional clinical trials targeting patients with SSc performed since September 2007. Two reviewers selected studies according to the prespecified eligibility criteria. Information on start date, country of origin, funding sources, phase of development, study design, (planned) sample size, enrollment status, outcomes, disease complication, and treatments investigated were retrieved and summarized.

Results. Among the 198 eligible studies identified (122 randomized controlled trials [RCTs; 62%]), 87 (30%) were conducted in Europe, 165 (83%) in a single country, and 81 (41%) were industry-funded. The majority of trials investigated pharmacologic treatments (75%), mostly nonbiotherapies (57%). RCTs were mostly 2-arm (82%) placebo-controlled (71%) studies with a median number of patients enrolled or planned to be enrolled of 40 (interquartile range 25–77 [range 10–586]). Twenty-one RCTs (17%) planned to enroll or enrolled >100 patients. Time to assess the primary outcome was found to be adequate in 29% to 50% of RCTs retrieved. Patients age >65 years were excluded in 14% of studies. SSc complications more frequently investigated in overall studies were skin thickness (26%), Raynaud's phenomenon/digital ulcers (24%), and interstitial lung disease (14%).

Conclusion. The SSc research landscape is dominated by small, short, and mainly placebo-controlled trials, especially investigating pharmacologic treatments. Some patients' needs continue to be neglected.

INTRODUCTION

Systemic sclerosis (SSc) is a systemic autoimmune disease of unknown etiology characterized by vasculopathy, immune system dysregulation, and fibrosis (1). In SSc, the accumulation of extracellular matrix and fibrosis can occur in almost every organ system (1), leading to a progressive loss of function. There are 2 subsets of scleroderma: limited cutaneous disease with slow accumulation of organ complications, and diffuse cutaneous disease characterized by rapidly progressive skin thickening and early internal organ involvement (2).

Although there has been some progress in understanding the pathophysiology of systemic inflammatory diseases, and a growing number of new molecules are being developed in the field of autoimmunity, the efficacy of the available treatments to slow or arrest fibrosis in SSc is limited (3,4), and the patients with the disease are still burdened by high disability (5), lower quality of life (6), and survival (7).

Performing clinical trials to evaluate treatments in patients with SSc is challenging for several reasons, such as low prevalence of the disease, heterogeneity of clinical phenotype, variability of disease progression, and difficulty in developing validated outcomes measures (8–10). An aggregate analysis of interventional research planned and carried out in such diseases as SSc may inform health-care providers and policy makers in coordinating research resources for the main needs of SSc patients.

We performed a systematic mapping of interventional clinical trials conducted and planned during the last 10 years in SSc. We investigated their main features, including the eligibility criteria, study design, comparisons, interventions, outcomes, location, and sponsors.

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SIGNIFICANCE & INNOVATIONS

- Randomized controlled trials (RCTs) conducted in systemic sclerosis during the last 10 years were mostly small placebo-controlled studies investigating pharmacologic treatments.
- Some disease complications have never been investigated in RCTs, likely due to the rarity of the disease and/or to the difficulties in identifying homogeneous groups of patients.
- The choice of patient-important outcomes as primary end points would represent the ideal option, but they are difficult to implement in real life.

MATERIALS AND METHODS

Search strategy. On February 22, 2018, we searched the International Clinical Trials Registry Platform (ICTRP) (11) for all records from September 2007 through February 2018 (trial registration became mandatory since September 2007). The ICTRP portal provides a single point of access to information about ongoing and completed clinical trials registered around the world. It provides a searchable database containing the trial registration data sets made available by many data providers, including ClinicalTrials.gov and the European Union Clinical Trials Register. A search strategy using the terms "systemic sclerosis" OR "scleroderma" OR "SSc" was performed.

Eligible criteria, data collection, and extraction. All interventional clinical trials targeting patients with SSc were included. We defined as interventional a clinical study in which participants are assigned to groups receiving ≥1 therapeutic intervention/treatment as determined by study protocol. We excluded fundamental research and diagnostic and cost-effectiveness studies. Two reviewers (MI and AB) independently checked the studies against the prespecified eligibility criteria. Disagreements were discussed by the authors to reach consensus. The same 2 reviewers independently extracted data from eligible studies by using a standardized form. Consensus was reached by discussion in case of disagreements.

General characteristics of trials. We assessed study characteristics that included country, start date, funding sources (industry, nonindustry), phase of development (0, I, II, III, IV), planned sample size, enrollment status (i.e., closed recruitment, recruiting, not yet recruiting, withdrawn), study design (i.e., nonrandomized controlled trials or randomized controlled trials [RCTs]), number of arms, type of intervention (pharmacologic [biotherapies, nonbiotherapies], nonpharmacologic [rehabilitation, procedure (i.e. surgery, ultraviolet therapy, injection of autologous adipose-derived stromal vascular fraction, stem cells transplantation), devices (12), and other]), and type of comparator (placebo, active intervention [pharmacologic or nonpharmacologic], usual care, or no intervention). We labeled as biotherapies each monoclonal antibody targeting immune cells and/or circulating cytokines. Data on the mechanism of action for each drug under investigation were also collected (13). A study was considered as being industry-funded if the sponsor or 1 of the collaborators was industry. Reasons for study withdrawal or early termination were identified in the ICTRP database or in the published reports, where available.

Eligibility criteria and population targeted in trials. The following data related to characteristics of patients as specified by eligibility criteria were collected: age (child [age <18 years], adults [ages 18–65 years], senior [age >65 years]), sex, disease subset (diffuse or limited disease according to LeRoy et al [2] or any), SSc classification criteria required to be included in the study (1980 American College of Rheumatology [ACR] criteria [14] or 2013 ACR/European League Against Rheumatism classification criteria [15]), autoantibody specificity (anti–Scl-70, anti-CENP, other), disease duration, refractoriness to other treatments, and the presence of ≥1 parameter of disease worsening.

Disease complications addressed by studies and classification of outcomes. We recorded the disease complications being investigated, grouping them in the following categories (16): skin thickness, Raynaud's phenomenon/digital ulcers, gastrointestinal, interstitial lung disease, pulmonary hypertension, heart dysfunction, joint/muscle function, renal, end-stage disease requiring transplantation, and other. The complication under investigation was defined according to an analysis of both eligibility criteria and primary outcome. For each RCT, we collected primary and secondary outcomes and we assessed the type of outcome (binary, continuous, and time-to-event). All outcomes were then independently classified by 2 of the authors (MI and AB) as patient-important outcomes or surrogate outcomes according to previous works on this topic (17,18). We classified patient-important outcomes as measures that directly impact on quality of life, such as major morbid events (e.g., death, end-stage lung disease, amputation) or minor morbid events (e.g., pain and functional status); surrogate outcomes were classified as measures that may indicate disease progression and increased risk for patient-important outcomes, or as assessed response to physiologic or laboratory testing without direct tangible effects on patients (e.g., capillaroscopic pattern, worsening of a respiratory parameter, etc.) (17,18). Consensus was reached by discussion in case of disagreement. Finally, we recorded the time frame of evaluation for each primary outcome of the RCTs. We classified as adequate the time frame of 12-weeks for interventions targeting Raynaud's phenomenon (8), 16 weeks for drugs given to heal digital ulcers (19), and 12 months for treatment of lung or skin fibrosis (20–23). The analysis was descriptive, continuous variables were expressed as median

(range, interquartile range [IQR]), and categorical variables were described with frequencies and percentages.

RESULTS

General characteristics of trials. Among the 198 eligible studies identified (see Supplementary Figure 1, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23817/abstract), 87 (30%) were conducted in Europe, 165 (83%) in a single country, and 117 (59%) were nonindustry-funded. The majority of trials investigated pharmacologic treatments (n = 148 [75%]), mostly nonbiotherapies (n = 113 [57%]). Late development (phase II/III, III, IV) was reported in 23% of trials (n = 47), middle development (phase I/II, II) in 35% (n = 70), and early development (phase 0, I) in 7% (n = 13). Table 1 shows the main features of overall studies and of RCTs included.

The 122 RCTs (62%) retrieved were mostly nonindustry funded (n = 70 [57%]), 2-arm (n = 100 [82%]), placebo-controlled (n = 87 [71%]) studies assessing the efficacy of pharmacologic treatments (n = 95 [78%]). The median number of patients enrolled or planned for enrollment was 40 (IQR 25–77 [range 10–586]). Twenty-one RCTs (17%) and 8 (6%) enrolled or planned to enroll >100 and >200 patients, respectively. Figure 1 shows the time trend of the interventions under study (A), and the class of the drugs (B) investigated in RCTs since 2008.

Four RCTs (3%) were withdrawn, and 7 (6%) ended prematurely (terminated) before completion. Withdrawal was reported to be due to unavailability of the device to be used in the trial (1 study), unwillingness of the principal investigator to proceed with the project (1 study), and unknown causes (2 studies). Reasons for early termination were poor tolerability/undesired events (3 studies), difficulties to enroll patients (2 studies), lack of efficacy (1 study), and principal investigator unavailability to complete the study (1 study).

Eligible criteria and population targeted. Studies generally included both sexes. Of 190 overall studies, patients age >65 years and children were excluded in 27 (14%) and in 175 (92%), respectively. Seventy-seven of 198 studies (39%) and 42 of 122 RCTs (34%) did not require the fulfillment of any validated classification criteria for SSc to enroll patients. A total of 140 studies (71%) included SSc patients from both disease subsets, 48 (24%) included only patients with diffuse disease, while only 7 (3%) targeted patients with limited disease. A minority of studies specifically investigated patients whose disease was refractory to previous treatments (n = 18 [9%]) or with ≥1 parameter of disease worsening (n = 21[10%]). Among the latter, 13 studies required skin worsening and 8 a deterioration of lung fibrosis. A specific antibody profile was required by 4 studies (antinuclear antibodies positivity in 1 study, anticentromere or antitopoisomerase I positivity in 1 study, anticentromere negativity in 1 study, and antitopoisomerase I positivity in 1 study).

Table 1. Characteristics of interventional studies on SSc patients from the World Health Organization International Clinical Trials Registry Platform*

Characteristic	Overall studies (n = 198)	RCTs (n = 122)
Start date		
Sep. 1 to Dec. 31, 2007	10 (5)	7 (6)
2008–2012	82 (41)	43 (35)
2013–2017	102 (52)	68 (56)
Jan. 1 to Feb. 22, 2018	4 (2)	4 (3)
Location of studies†		
North America	118 (40)	51 (30)
Europe	87 (30)	56 (33)
Asia	58 (20)	36 (21)
South America	16 (5)	13 (8.5)
Oceania	10 (3)	8 (5)
Africa	5 (1.5)	4 (2)
Unclear	1 (0.5)	1 (0.5)
Type of intervention		
Pharmacologic	148 (75)	95 (78)
Nonbiotherapies	113 (57)	72 (59)
Biotherapies	35 (18)	23 (19)
Nonpharmacologic	50 (25)	27 (22)
Rehabilitation	10 (5)	9 (7)
Procedure	29 (14.5)	10 (8)
Devices	3 (1.5)	2 (2)
Other	8 (4)	6 (5)
Study design		
Non-RCTs	76 (38)	–
RCTs	122 (62)	–
Parallel group	122 (62)	113 (93)
Crossover	12 (6)	9 (7)
Type of comparator		
Placebo	–	87 (71)
Active, pharmacologic	–	14 (11)
Active, nonpharmacologic	–	7 (6)
Usual care	–	8 (7)
No intervention	–	5 (4)
Other	–	1 (1)
Phase of development		
Early (0, I)	13 (7)	5 (5)
Middle (I/II, II)	70 (35)	50 (40)
Late (II/III, III, IV)	47 (23)	34 (28)
Not reported/not applicable	68 (35)	33 (27)
Status of recruitment		
Closed recruitment‡	95 (48)	59 (48)
Recruiting/ongoing	61 (31)	34 (28)
Not yet recruiting	22 (11)	18 (15)
Withdrawn	6 (3)	4 (3)
Unknown	14 (7)	7 (6)
No. of patients planned for inclusion or included per study (median, range)	34 (1–586)	40 (10–586)

* Values are the number (%) unless indicated otherwise. RCTs = randomized controlled trials.
† Multiple answers were possible.
‡ Completed recruitment or terminated studies.

Twenty-four of 34 RCTs (70%) targeting drugs for skin fibrosis required patients to have a prespecified modified Rodnan skin score to be included, ranging from a median lower score of 10 (IQR 10–15; lower threshold) to a median higher score of 51 (IQR

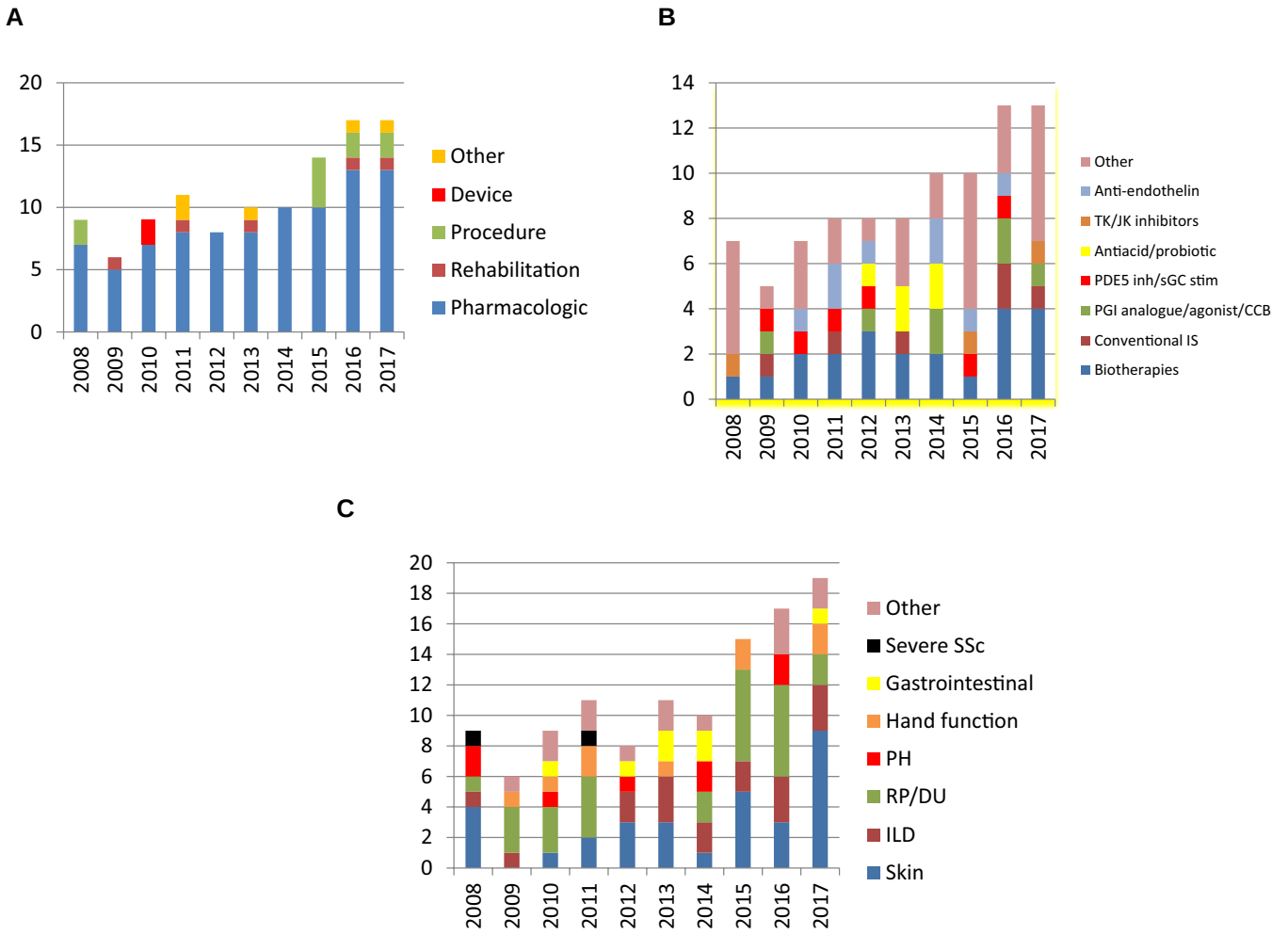

Figure 1. Evolution over time of the number of randomized controlled trials, by type of intervention (**A**), class of drug (**B**), and SSc complication investigated (**C**). TK = tyrosine kinase; JK = Janus kinase; PDE5 inh = phosphodiesterase 5 inhibitors; sGC stim = soluble guanylate cyclase stimulator; PGI = prostacyclin; CCB = calcium channel blocker; IS = immunosuppressor; SSc = systemic sclerosis; PH = pulmonary hypertension; RP/DU = Raynaud's phenomenon/digital ulcers; ILD = interstitial lung disease.

35–51; higher threshold). Table 2 shows the main features of the population included in RCTs. Additional data are shown in Supplementary Table 1, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23817/abstract.

Disease complications addressed by studies. SSc complications more frequently investigated by overall studies were skin thickness (n = 52 [27%]), Raynaud's phenomenon/digital ulcers (n = 47 [24%]), and interstitial lung disease (n = 28 [14%]). Figure 1C shows the SSc complications under investigation in RCTs. Figures 2 and 3 show the networks of planned/conducted RCTs for the main SSc complications.

Classification of RCT outcomes. In 44 RCTs (36%), the primary outcome was not considered patient-important, and 12 studies (10%) did not have any patient-important outcome as primary or secondary outcome. When focusing only on larger trials, we found that the percentage of patient-important outcomes among the primary outcome was 86% (n = 18 of 21) for studies with >100 patients, and 87% (n = 7 of 8) with those with >200 patients. The median time and the percentage of studies with an adequate time frame to assess the primary outcome for the main complications investigated are shown in Table 2.

DISCUSSION

In the current study we provide a comprehensive description of interventional studies conducted and being conducted in the field of SSc since a trial registration became mandatory. Most of the retrieved studies came from Europe and North America, were nonindustry funded, and were mostly small studies investigating pharmacologic interventions.

Table 2. Features of population included in randomized controlled trials (n = 122)*

Population	Values
Age, years	
Adults and seniors (age >65)	88 (72)
Adults (ages 18–65)	18 (15)
All ages	11 (9)
Children and adults	2 (2)
Unclear	3 (2)
SSc classification criteria fulfillment not required	42 (34)
Disease subset	
Both subsets	83 (68)
Only diffuse SSc patients	32 (26)
Only limited SSc patients	4 (3.5)
Unclear	3 (2.5)
Any disease duration	80 (65)
Condition being evaluated†	
Skin thickness	34 (27)
Raynaud's phenomenon/digital ulcers	31 (24)
Interstitial lung disease	19 (15)
Hand function	11 (9)
Pulmonary hypertension	8 (6)
Gastrointestinal tract	7 (5)
Severe or end-stage disease	2 (2)
Renal disease	1 (1)
Calcinosis	1 (1)
Other	13 (10)
Classification of important outcomes	
Patient-important outcomes (PIOs)	225 (71)
Surrogate outcomes	112 (29)
No. of studies with ≥1 PIO	110 (90)
No. of studies with ≥1 PIO as primary outcome	78 (64)
Time to primary outcome assessment, median (range) days	
Interstitial lung disease	258 (168–730)
Skin thickness	181 (90–730)
Digital ulcers (healing)	101 (56–300)
Raynaud's phenomenon	56 (28–84)
Primary outcome for each SSc complication, no./total no. (%)‡	
Interstitial lung disease	7/16 (44)
Skin thickness	8/28 (29)
Digital ulcers (healing)	3/6 (50)
Raynaud's phenomenon	1/4 (25)

* Values are the number (%) unless indicated otherwise. SSc = systemic sclerosis.
† Multiple answers were possible.
‡ With the time point considered to be adequate.

The analysis of eligibility criteria allows us to draw some conclusions. First, as often happens (24), older patients were underrepresented in potential eligible populations. Scarce attention was also paid to patients with limited SSc as a distinct group. Moreover, it should be highlighted that some trials were prematurely closed because of difficulties in enrolling patients. In this regard, we can speculate that among the factors potentially hindering patient recruitment, the selection of strict eligibility criteria has likely played an important role. The use of entry criteria that are too selective in RCTs is not uncommon (25) and has already been pointed out in SSc (26). In 2008, Villela et al (26) showed that only a minority of SSc patients from the Canadian Scleroderma Research Group could have been potentially recruited in RCTs conducted between 1958 to 2006. They identified disease duration and disease subsets as the main reasons for patient exclusion. The main barriers to enrollment in RCTs conducted since that time remain to be investigated to provide further guidance for future trials design.

The choice of criteria for patients to be enrolled in clinical trials on skin or lung fibrosis is challenging (27), because these complications can display a varied course, ranging from a quiescent or slow progressing disease to forms having a rapidly devastating worsening. We found that the inclusion criteria of retrieved studies rarely took into account parameters of disease progression, allowing the potential enrollment of patients with stable longstanding fibrosis. In addition, studies targeting drugs for skin fibrosis almost never indicated the limit of the upper skin score in eligibility criteria, allowing patients with a very high skin score, and therefore at high risk to spontaneously improve, to be included. Actually, we know that most of the patients with higher skin scores (>22–25) tend to improve without any treatment (28,29) and that an upper threshold of skin score between 18 and 25 has the best performance in identifying progressors over regressors (28). Taken together, these findings suggests that there is still room for improvement in the selection of eligibility criteria for SSc patients being recruited in RCTs, particularly for those investigating drugs for skin or lung fibrosis (30).

Skin thickness, Raynaud's phenomenon, digital ulcers, and lung complications were the main targets of studies retrieved. By contrast, other SSc manifestations such as gastrointestinal, cardiac, articular, or calcinosis, for which treatments routinely used are still unsatisfactory and based only on the physician's experience, have been largely neglected. Gastrointestinal disease occurs in almost every SSc patient and is responsible for sleep disturbance, depression, overall poor quality of life, and approximately 10% of mortality (4,31–33). Calcinosis is difficult to manage and is often associated with chronic pain, risk of soft tissue infection, and functional impairment (34). Cardiac disease is recognized as a poor prognostic factor and a leading cause of death (4). The identification of this gap in research should hopefully help to increase the attention of researchers toward these poorly investigated manifestations. The advocated availability in the future of prognostic indicators, including clinical and laboratory features, genomic or proteomic markers helping to identify patients with high risk to develop such complications, could hopefully permit designing tailored RCTs needing a smaller sample size to discern a treatment effect.

Most studies investigated pharmacologic treatments. Besides symptomatic drugs to control Raynaud's phenomenon or gastrointestinal symptoms, the main classes of drugs investigated were monoclonal antibodies, analogs or agonists of prostacyclin, and drugs regulating the nitric oxide pathways. Luckily, even if trials assessing rehabilitation strategies are still

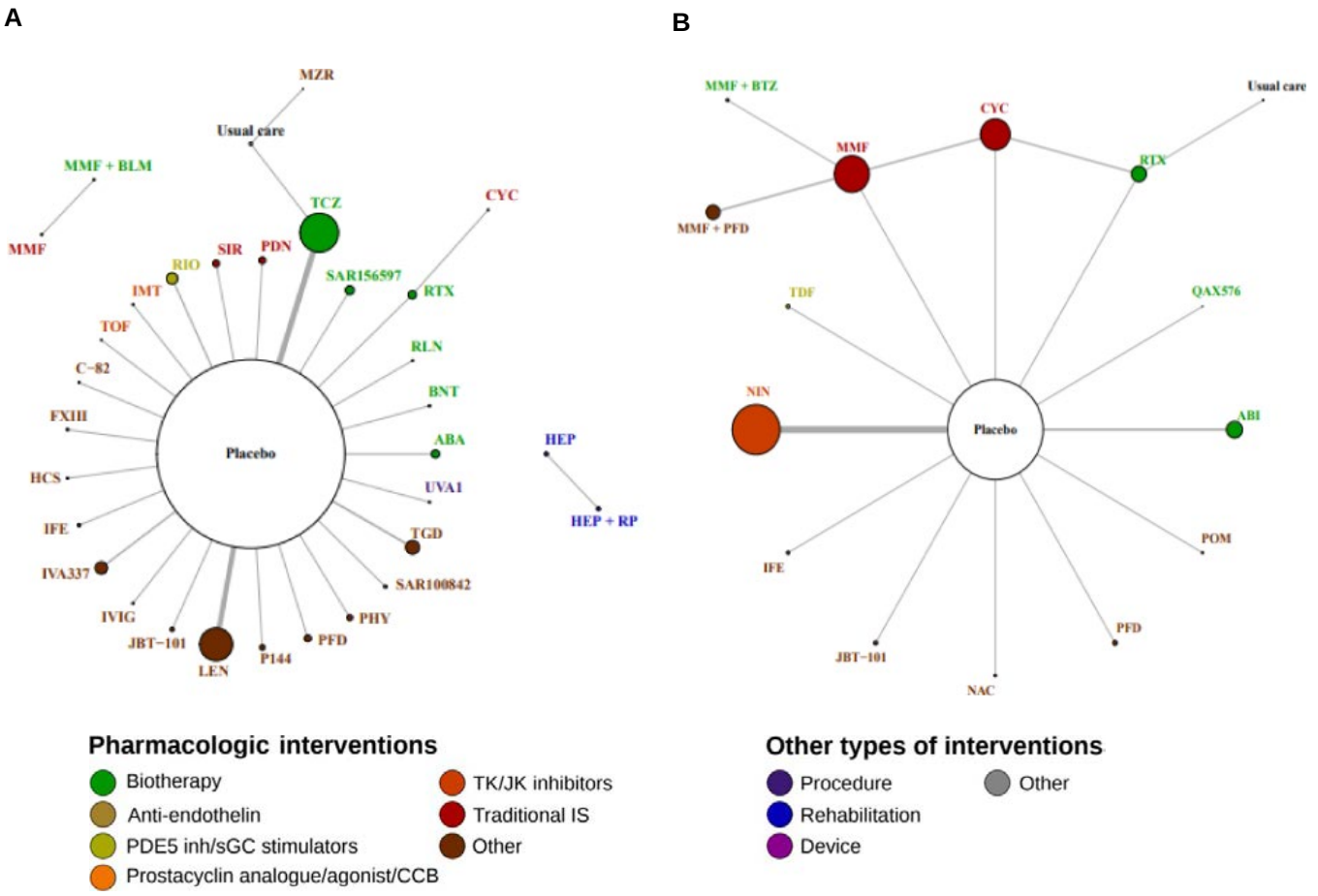

Figure 2. Networks of RCTs planned/conducted for **A**, skin thickness, and **B**, interstitial lung disease. The dimension of the circle is proportional to the number of patients enrolled/planned to be enrolled for each drug. The thickness of the connector is proportional to the number of patients enrolled/planned to be enrolled for each comparison. AA = alginic acid; ABA = abatacept; ABI = abituzumab; ACC = arm cranking + cycling; ACO = acotinamide hydrochloride; ALP = alprostadil; AMB = ambrisentan; API = apixaban; ATO = atorvastatin; BLM = belimumab; BMS-986020 = BMS-986020; BNT = brentuximab; BOS = bosentan; Botox = botulinum toxin; BTZ = bortezomib; BYS = bypass prior to sympathectomy during the surgical procedure; C-82 = C-82; CYC = cyclophosphamide; DLT = diltiazem; CMF = dimethyl fumarate; DOMP = domperidone; FIL = filgrastim; FLU = fludarabine; FLV = flu vaccine; FXIII = fibrogammin P; GB = ginkgo biloba; GHR = ghrelin; GSK2330811 = GSK2330811; HCS = hyperimmune caprine serum; HD = high dose; HE = hand exercise; HEP = home exercise program; HS = hand splint; HSCT = hematopoietic stem cells transplantation; IFE = ifetroban; IMP = Internet-based self-management program; IMT = imatinib; IVA337 = IVA337; IVIG = intravenous immunoglobulins; JBT-101 = JBT-101; LD = low dose; LEN = lenabasum; LEU = leuprolide; MCT = macitentan; MD = medium dose; MEDI-551 = MEDI-551; MEDI7734 = MEDI7734; MG1 = massage on hand (without glove) 15 minutes, then thermography test and a nylon fabric glove is worn on the hand for 10 minutes, then remove the glove for the last thermography test; MG2 = a nylon fabric glove is worn on the hand during the 15-minute massage (massage together with glove: control treatment) and remove the glove for thermography test (hand thermal imager), wearing the glove again for 10 minutes, then remove the glove for the last thermography test; MHE = traditional Thai massage, hand stretching exercise; ML = manual lymph drainage; MMF = mycophenolate mofetil; MPPT = methylprednisolone pulse therapy; MQX-503 = topical nitroglycerin; MSC = mesenchymal stromal cells; MZR = mizoribine; NAC = N-acetylcysteine; NIF = nifedipine; NIN = nintedanib; NIT = nitroglycerine; NVG = neovasculgen; OME = omeprazole; ORM-12741 = ORM-12741; OZO = ozone; P144 = P144; PDN = prednisone; PF-00489791 = PF-00489791; PFD = pirfenidone; PHY = *Physalis angulata*; POM = pomalidomide; PRI = pressure-relieving insole; PRO = probiotic; QAX576 = QAX576; rATG = rabbit antithymocyte globulin; RIO = riociguat; RLN = rilonacept; ROS = rosuvastatin; RP = rehabilitation program; RTX = rituximab; SAR100842 = SAR100842; SAR156597 = SAR156597; SB = scleroderma book; SBY = sympathectomy prior to bypass during the surgical procedure; SIL = sildenafil; SIR = sirolimus; STS = sodium thiosulfate: SVF = stromal vascular fraction; SXP = selexipag; TCZ = tocilizumab; TDF = tadalafil; TGD = terguride; TOF = tofacitinib; TRE = treprostinil; TRI = trimebutine; UVA1 = ultraviolet light; VIP = aviptadil (vasoactive intestinal peptide); WB = wax bath; WG = wearing gloves; ZBT = zibotentan.

few, an increasing number of trials investigating interventions to improve hand function have been registered in previous years, maybe due to a growing awareness of the importance of behavioral and rehabilitative practices in the management of SSc patients (35). Most of the RCTs were parallel 2-arm studies having placebo as a comparator. The extensive use of the

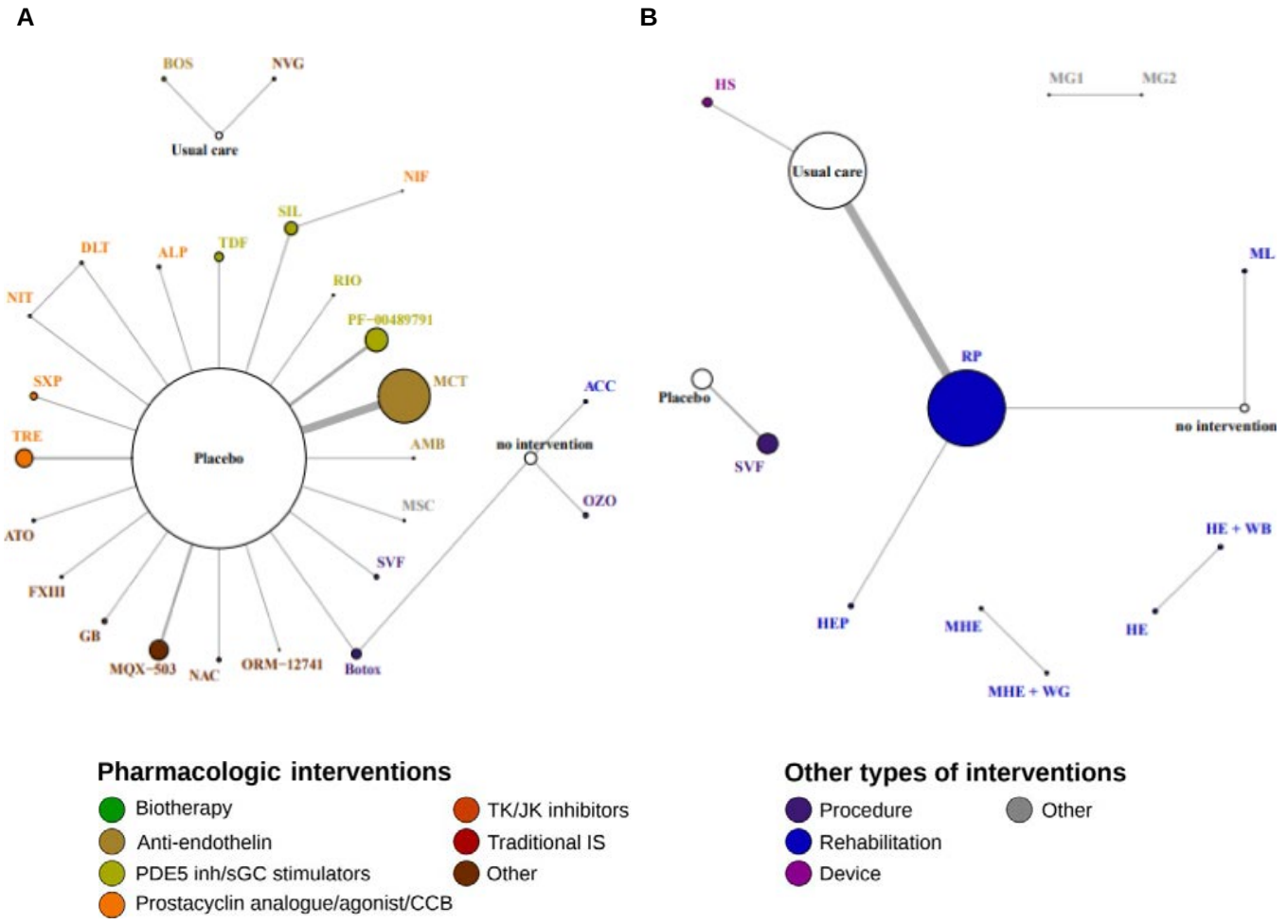

Figure 3. Networks of RCTs planned/conducted for **A**, Raynaud's phenomenon/digital ulcers, and **B**, hand function. The dimension of the circle is proportional to the number of patients enrolled/planned to be enrolled for each drug. The thickness of the connector is proportional to the number of patients enrolled/planned to be enrolled for each comparison. See Figure 2 caption for abbreviations.

placebo suggests the lack of efficacious treatments for most SSc complications. Given the routine use in clinical practice of treatments whose efficacy has never been demonstrated, the use of placebo in newly designed trials could also have represented a barrier to the recruitment, due to a potential patient's reluctance to receive it. In this context, different trial designs such as add-on, early-escape, and randomized withdrawal designs might also be considered (8,16).

As far as RCT size, the estimated number of patients enrolled or anticipated to be enrolled was often small. Moreover, the duration of trials was also not always as long as expected to answer important clinical questions. As we know, the recommended time to follow up SSc patients depends on the target complication under investigation. For example, a 12-week trial would be adequate to study Raynaud's phenomenon (16), or a 16–24 week study to assess drugs given to heal digital ulcers (19). Due to the slow turnover of collagen fibers, a longer trial duration (12–24 months) would be needed to investigate the role of treatments for lung or skin fibrosis (20–23). The time to assess the primary outcome was found to be adequate in 25% to 60% of studies, depending on the complication investigated.

The tendency to perform mainly small studies could mirror the difficulty to enroll patients with such a rare disease, but can also be explained by the fragmentation of research funding as well as the possible lack of interest to work in larger networks due to the need to incentivize individual projects over larger collaborative studies.

Finally, it should be emphasized that approximately one-third of the studies did not have a patient-important outcome among the primary outcomes. These findings deserve a further comment. While performing trials with hard outcomes like death, hospitalization, etc., would represent an ideal scenario, the slow-progressing SSc course and the rarity and heterogeneity of the disease impose a necessary compromise in the selection of primary end points. In this context, surrogate end points able to capture chronic disease progression with a demonstrable linkage to patient-centered outcomes could represent the more realistic and meaningful tool (9,36).

This study has some limitations. First, we could have undoubtedly missed some clinical trials not registered in online databases searched. Second, we may not have detected trials on pulmonary hypertension where scleroderma patients are generally labeled as "connective tissue patients." Third, some important trial features could have been reported only in final publication and not in online databases and consequently were not analyzed in the current article.

In conclusion, as observed in other fields (24), the SSc research landscape is dominated by small trials, especially investigating pharmacologic treatments. Unfortunately, some patients' needs continue to be neglected. The awareness of state-of-the-art research might represent an opportunity to further encourage collaboration and boost clinical research in the field.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Iudici had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Iudici, Bafeta, Atal, Ravaud.
Acquisition of data. Iudici, Bafeta.
Analysis and interpretation of data. Iudici, Bafeta, Atal, Ravaud.

REFERENCES

1. Gabrielli A, Avvedimento EV, Krieg T. Scleroderma. N Engl J Med 2009;360:1989–2003.
2. LeRoy EC, Black C, Fleischmajer R, Jablonska S, Krieg T, Medsger TA Jr, et al. Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. J Rheumatol 1988;15:202–5.
3. Morrisroe K, Frech T, Schniering J, Maurer B, Nikpour M. Systemic sclerosis: the need for structured care. Best Pract Res Clin Rheumatol 2016;30:3–21.
4. Steen VD, Medsger TA. Changes in causes of death in systemic sclerosis, 1972-2002. Ann Rheum Dis 2007;66:940–4.
5. Singh MK, Clements PJ, Furst DE, Maranian P, Khanna D. Work productivity in scleroderma: analysis from the University of California, Los Angeles Scleroderma Quality of Life Study. Arthritis Care Res (Hoboken) 2012;64:176–83.
6. Frantz C, Avouac J, Distler O, Amrouche F, Godard D, Kennedy AT, et al. Impaired quality of life in systemic sclerosis and patient perception of the disease: a large international survey. Semin Arthritis Rheum 2016;46:115–23.
7. Elhai M, Meune C, Boubaya M, Avouac J, Hachulla E, Balbir-Gurman A, et al. Mapping and predicting mortality from systemic sclerosis. Ann Rheum Dis 2017;76:1897–905.
8. Gordon JK, Domsic RT. Clinical trial design issues in systemic sclerosis: an update. Curr Rheumatol Rep 2016;18:38.
9. Pope JE. Trial methodology in scleroderma: avoiding a shot in the dark. Rheumatology (Oxford) 2017;56 Suppl:v1–3.
10. Matucci-Cerinic M, Steen VD, Furst DE, Seibold JR. Clinical trials in systemic sclerosis: lesson learned and outcomes. Arthritis Res Ther 2007;9 Suppl:S7.
11. World Health Organization. International clinical trials registry platform. URL: http://apps.who.int/trialsearch/.
12. World Health Organization. Medical devices: definitions. URL: http://www.who.int/medical_devices/definitions/en/.
13. DrugBank. Version 5.1.0, released 2018-04-02. URL: https://www.drugbank.ca.
14. Subcommittee for Scleroderma Criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. Preliminary criteria for the classification of systemic sclerosis (scleroderma). Arthritis Rheum 1980;23:581–90.
15. Van den Hoogen F, Khanna D, Fransen J, Johnson SR, Baron M, Tyndall A, et al. 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum 2013;65:2737–47.
16. Khanna D, Furst DE, Allanore Y, Bae S, Bodukam V, Clements PJ, et al. Twenty-two points to consider for clinical trials in systemic sclerosis, based on EULAR standards. Rheumatology (Oxford) 2015;54:144–51.
17. Ferreira-Gonzalez I, Busse JW, Heels-Ansdell D, Montori VM, Akl EA, Bryant DM, et al. Problems with use of composite end points in cardiovascular trials: a systematic review of randomized controlled trials. BMJ 2007;334:786.
18. Gandhi GY, Murad MH, Fujiyoshi A, Mullan RJ, Flynn DN, Elamin MB, et al. Patient-important outcomes in registered diabetes trials. JAMA 2008;299:2543–9.
19. Matucci-Cerinic M, Denton CP, Furst DE, Mayes MD, Hsu VM, Carpentier P, et al. Bosentan treatment of digital ulcers related to systemic sclerosis: results from the RAPIDS-2 randomised, double-blind, placebo-controlled trial. Ann Rheum Dis 2011;70:32–8.
20. Tashkin DP, Elashoff R, Clements PJ, Goldin J, Roth MD, Furst DE, et al. Cyclophosphamide versus placebo in scleroderma lung disease. N Engl J Med 2006;354:2655–66.
21. Nannini C, West CP, Erwin PJ, Matteson EL. Effects of cyclophosphamide on pulmonary function in patients with scleroderma and interstitial lung disease: a systematic review and meta-analysis of randomized controlled trials and observational prospective cohort studies. Arthritis Res Ther 2008;10:R124.
22. Seibold JR, Korn JH, Simms R, Clements PJ, Moreland LW, Mayes MD, et al. Recombinant human relaxin in the treatment of scleroderma: a randomized, double-blind, placebo-controlled trial. Ann Intern Med 2000;132:871–9.
23. Le EN, Wigley FM, Shah AA, Boin F, Hummers LK. Long-term experience of mycophenolate mofetil for treatment of diffuse cutaneous systemic sclerosis. Ann Rheum Dis 2011;70:1104–7.
24. Alexander KP, Kong DF, Starr AZ, Kramer J, Chiswell K, Tasneem A, et al. Portfolio of clinical research in adult cardiovascular disease as reflected in ClinicalTrials.gov. J Am Heart Assoc 2013;2:e000009.
25. Kennedy-Martin T, Curtis S, Faries D, Robinson S, Johnston J. A literature review on the representativeness of randomized controlled trial samples and implications for the external validity of trial results. Trials 2015;16:495.
26. Villela R, Yuen SY, Pope JE, Baron M, and the Canadian Scleroderma Research Group. Assessment of unmet needs and the lack of generalizability in the design of randomized controlled trials for scleroderma treatment. Arthritis Rheum 2008;59:706–13.
27. Merkel PA, Silliman NP, Clements PJ, Denton CP, Furst DE, Mayes MD, et al. Patterns and predictors of change in outcome measures in clinical trials in scleroderma: an individual patient meta-analysis of 629 subjects with diffuse cutaneous systemic sclerosis. Arthritis Rheum 2012;64:3420–9.
28. Dobrota R, Maurer B, Graf N, Jordan S, Mihai C, Kowal-Bielecka O, et al. Prediction of improvement in skin fibrosis in diffuse cutaneous systemic sclerosis: a EUSTAR analysis. Ann Rheum Dis 2016;75:1743–48.
29. Maurer B, Graf N, Michel BA, Müller-Ladner U, Czirják L, Denton CP, et al. Prediction of worsening of skin fibrosis in patients with

diffuse cutaneous systemic sclerosis using the EUSTAR database. Ann Rheum Dis 2015;74:1124–31.
30. Allanore Y, Distler O. Advances in cohort enrichment shape future of trial design. Nat Rev Rheumatol 2015;11:72–4.
31. Milette K, Hudson M, Körner A, Baron M, Thombs BD. Canadian Scleroderma Research Group. Sleep disturbances in systemic sclerosis: evidence for the role of gastrointestinal symptoms, pain and pruritus. Rheumatology (Oxford) 2013;52:1715–20.
32. Bodukam V, Hays RD, Maranian P, Furst DE, Seibold JR, Impens A, et al. Association of gastrointestinal involvement and depressive symptoms in patients with systemic sclerosis. Rheumatology (Oxford) 2011;50:330–4.
33. Frech TM, Mar D. Gastrointestinal and hepatic disease in systemic sclerosis. Rheum Dis Clin North Am 2018;44:15–28.
34. Valenzuela A, Song P, Chung L. Calcinosis in scleroderma. Curr Opin Rheumatol 2018;30:554–561.
35. Willems LM, Vriezekolk JE, Schouffoer AA, Poole JL, Stamm TA, Boström C, et al. Effectiveness of nonpharmacologic interventions in systemic sclerosis: a systematic review. Arthritis Care Res (Hoboken) 2015;67:1426–39.
36. Khanna D, Seibold J, Goldin J, Tashkin DP, Furst DE, Wells A. Interstitial lung disease points to consider for clinical trials in systemic sclerosis. Rheumatology (Oxford) 2017;56 Suppl:v27–32.

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Erratum

An error was detected in the article by Power et al in the September 2019 issue of *Arthritis Care & Research* (pages 1178–1185). In the Methods of the abstract on page 1178, the sentence listing the sample sizes should have read "Participants were pre-surgical patients with end-stage knee (n = 539), hip (n = 436), and spine (n = 151) OA."

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