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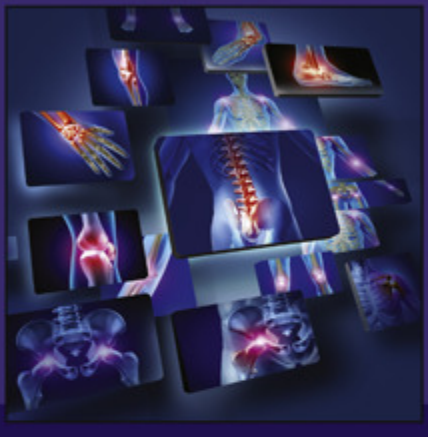

RHEUMATIC DISEASES IN OLDER ADULTS

CONSULTING EDITOR
MICHAEL H. WEISMAN

EDITORS
JAMES D. KATZ
BRIAN WALITT

August 2018

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Rheumatic Diseases in Older Adults

Editors

JAMES D. KATZ
BRIAN WALITT

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Foreword

Rheumatic Diseases in Older Adults

Michael H. Weisman, MD
Consulting Editor

This is a unique issue, and much thanks goes to the team of Katz and Walitt for their ability to focus scholarly attention to a very practical matter in our practice environment. Alan Baer and Brian Walitt address sicca symptoms and signs in the older adult, emphasizing the very common findings of dry eye and dry mouth in this population and the need to make a specific diagnosis of Sjögren syndrome (SS) within this background. Direct to consumer advertising has increased awareness of these conditions, and it behooves the Rheumatologist to be able to recognize SS among the many causes of sicca. Diagnosis of SS depends on the demonstration of autoimmunity: it requires the presence of anti-SS A and/or anti-SS B antibodies, or a minor salivary gland biopsy. Drs Gupta, Dhillon, and Hasni review the major aspects of sarcopenia, including definition, prevalence, pathophysiology, diagnosis, and management. The growing impact of this condition is extremely important not only clinically but also for how it effects health resource utilization. Mandana Hashefi points out that we have known about the association of rheumatic disorders and malignancies for over 100 years, but understanding causality remains opaque. Certain malignancies appear with greater incidence in our diseases, and the clinical associations and risks are outlined with unusual depth and clarity by Dr Hashefi. She points out very clearly that musculoskeletal syndromes can be a presenting manifestation of neoplasia, and it is critical to be suspicious and vigilant in these clinical situations. Drs Alejandro and Constantinescu review the diagnosis and management of osteoporosis in the older adult with special emphasis on individualizing management and balancing risks and benefits of medications.

Katharine Alter, Ana Acevedo, and Adrienne Jackson review and update very useful information on how to diagnosis and manage regional rheumatic disorders, emphasizing the whole patient within the aging process. This article gives the reader an understanding of the rationale behind the rehabilitation approach to this fastest

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growing proportion of the patient population seen in our medical facilities. Drs Mackey, Kuller, and Moreland point out the ever-present underestimation of cardiovascular risk in our rheumatoid arthritis patients by relying on traditional risk factors; they identify inflammation as the major target for risk reduction and the possibility of identifying new lipid moieties that better reflect this association. Drs El-Zawawy and Mandel address the increasing clinical significance of gout in the elderly with its unique diagnostic features and clear unacceptable functional liabilities. The importance of urate-lowering therapy in this population is suitably emphasized. Drs Lafian and Torralba emphasize the diagnostic and therapeutic challenges of lumbar spinal stenosis in the older age group, pointing out the ever-present disparities between imaging and signs and symptoms. Nora Taylor makes the excellent point that assessment of knee osteoarthritis in the elderly requires a comprehensive approach involving patient preferences, comorbidities, and functional status. Drs Betancourt, Biehl, Katz, and Subedi make the cogent argument that older patients with rheumatic diseases are at increased risk for therapeutic misadventures because of polypharmacy, age-related pharmacodynamic and pharmacokinetic changes, and most importantly, health literacy and, not surprisingly, provider biases. These experienced clinicians provide excellent tips for help in this difficult area.

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Preface

Rheumatic Diseases in Older Adults

James D. Katz, MD Brian Walitt, MD, MPH
Editors

We are pleased to present this special issue of *Rheumatic Disease Clinics of North America* that is devoted to Older Adults. It is an extension of our earlier work already published in the cousin series, *Clinics in Geriatric Medicine.*[1] To this end, we have reassembled and enhanced the broad range of expertise that will now serve to highlight the latest diagnostic and therapeutic information in the field. Our agenda has not been to reinvent a general overview of geriatric rheumatology but rather to hone in on pragmatic as well as up and coming musculoskeletal issues facing rheumatologists.

Arthritis-related disability can reflect either aging into disability or aging with disability.[2] In these situations, symptom management commonly involves specialists such as rheumatologists. Among the identified unmet needs of rheumatology are (a) better provider education in clinical management, and (b) "improved understanding of targeting of specific therapies."[3] Moreover, it has been over a decade since van Lankveld, Franssen, and Stenger called for "a gerontorheumatological service aimed at patients with musculoskeletal conditions."[4] To these ends, we believe the time is right to usher forward the efforts to bridge rheumatology and gerontology by crafting this issue of the *Rheumatic Disease Clinics of North America*.

The choice of contributors herein reflects our bias that not only rheumatologists but also other academicians who are involved in the rheumatologic aspects of aging are well suited to address the impact of musculoskeletal issues affecting function and mobility. Hence, within these pages, you will find not only clinical pearls helping the practitioner to navigate underappreciated aspects of pharmacotherapeutics but also, for example, a nuanced rheumatologic perspective on sarcopenia and an in-depth review of immune dysregulation in aging.

As guest editors, we have encouraged broad thinking among our authorship. Our contributors have been tasked not to lose sight of the principle of aging in place while at the same time aiming to drive forward thoughtful discussion within the medical

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community.[5] Furthermore, we have encouraged our contributors to remain grounded and to keep sight of the pragmatic and clinical consequences of their respective areas of expertise. Therefore, interspersed among these pages may be found both philosophical perspectives and potential policy-shaping research agendas. As such, we hope this issue serves to further the study of quality of life in an aging demographic. Finally, we hope that by invoking rheumatologic insight we have broadened the clinical horizon sufficiently so as to challenge the perspectives of educators, practitioners, and academicians, alike.

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2. Choi S. Midlife adults with functional limitations: comparison of adults with early- and late-onset arthritis-related disability. Disabil Health J 2018;11(3):374–81. [Epub ahead of print].
3. Winthrop KL, Strand V, van der Heijde D, et al. The unmet need in rheumatology: reports from the targeted therapies meeting 2017. Clin Immunol 2018;186:87–93.
4. van Lankveld W, Franssen M, Stenger A. Gerontorheumatology: the challenge to meet health-care demands for the elderly with musculoskeletal conditions. Rheumatology (Oxford) 2005;44(4):419–22.
5. Morley JE. Aging successfully: the key to aging in place. J Am Med Dir Assoc 2015;16(12):1005–7.

Erratum

The forthcoming issues page in the May 2018 issue of *Rheumatic Disease Clinics* (Volume 44, Issue 2) incorrectly listed the August 2018 issue as Medical Practice Challenges for the Rheumatologist Herb Baraf, Editor, instead of "Rheumatic Diseases in Older Adults" edited by James D. Katz and Brian Wallitt.

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Pharmacotherapy Pearls in Rheumatology for the Care of Older Adult Patients

Focus on Oral Disease-Modifying Antirheumatic Drugs and the Newest Small Molecule Inhibitors

Blas Y. Betancourt, MD[a,*], Ann Biehl, MS, PharmD, BCPS[b], James D. Katz, MD[a], Ananta Subedi, MD[a]

KEYWORDS

• Geriatrics • DMARDs • Rheumatology • Rheumatoid arthritis • Tofacitinib • Apremilast

KEY POINTS

- Older patients with rheumatic disorders are at increased risk for therapeutic misadventure because of age-related pharmacokinetic and pharmacodynamic changes, polypharmacy, comorbidities, impaired health literacy secondary to decreased cognition, and provider age bias.
- Rheumatologists along with other members of the allied health care team can most effectively minimize the risk for medication-related adverse reactions in older patients.
- Familiarity with dosing, monitoring, adverse reactions, medication interactions, and amelioration strategies can improve the safety of disease-modifying antirheumatic drugs in the older rheumatology patient.

INTRODUCTION

Providing safe and effective pharmacotherapy to the geriatric patient population is an ongoing struggle for health care providers. The incidence of rheumatologic disorders increases with advancing age. Recent National Health Interview Survey data

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(2013–2015) observed a prevalence of physician-diagnosed arthritis among adults aged 65 years and older approaches 50% with 44% of these patients having related activity limitation.[1] It is estimated that rheumatoid arthritis (RA) affects 0.5% to 1% of the adult population in developed countries. This translates to approximately 1.3 million Americans, with an increasing prevalence with advancing age.[2]

Oral disease-modifying antirheumatic drugs (DMARDs) are not only effective in reducing morbidity and improving quality of life but can also have a positive impact on mortality.[3] However, DMARDs alter the host immune system and could create a risk of significant adverse events including infection and malignancy. A rheumatologist involved in the care of the elderly should be aware of specific adverse reactions and drug interactions associated with the use of oral DMARDs.

Older patients are at increased risk for adverse drug reactions. Budnitz and colleagues[4] found individuals older than the age of 65 were more likely than younger persons to have adverse drug reactions requiring emergency room visits and hospitalization. Such therapeutic misadventures in geriatric patients are caused by age-related changes in pharmacokinetics and pharmacodynamics, polypharmacy contributing to increased risk of clinically significant drug-drug interactions, and alterations in cognitive faculties that impair health literacy and therapeutic adherence.[5–11] These problems are likely compounded by age bias, manifesting as a reluctance to aggressively treat older patients, and economic barriers.[12,13] Management of rheumatologic conditions also carries special risk because of rapidly evolving use of novel therapeutic agents with limited data guiding their use in geriatric patients.

This article provides an update regarding commonly used oral DMARDs for the treatment of inflammatory arthritis, including methotrexate (MTX), hydroxychloroquine (HCQ), sulfasalazine (SSZ), and leflunomide, and the newer oral antirheumatic agents tofacitinib and apremilast. Although nonsteroidal anti-inflammatory drugs, prednisone, and injectable biologic agents are commonly used in the management of inflammatory arthritis, these are outside the scope of this article.

AGE-RELATED CHANGES IN PHARMACOKINETICS AND PHARMACODYNAMICS

Pharmacokinetics is the study of drug absorption, distribution, metabolism, and excretion in the body. Geriatric patients experience physiologic changes at every step of the pharmacokinetic process.[7,9] However, understanding of the age-related changes on pharmacokinetic properties of particular medications has been hampered by the general lack of inclusion of older adults in clinical trials and drug-specific pharmacokinetic studies. The most clinically significant pharmacokinetic alteration in the geriatric population is a decline in renal function that decreases metabolite excretion. Several commonly used antirheumatic medications, such as MTX, require monitoring of renal function.

Pharmacodynamics is the study of the biochemical and physiologic effects of drugs in the body. The pharmacodynamic changes with aging are more difficult to study and less characterized than pharmacokinetic alterations. In general, the response in elderly is less predictable and subject to more interindividual variability.[11] Aging patients experience changes at multiple levels including receptor, signal transduction, or homeostatic mechanisms. This not only affects the effectiveness but also the risk of adverse reactions. For example, a decrease in cell density and cell proliferation in the bone marrow in elderly individuals[7] makes these patients especially sensitive to the hematologic side effects of MTX.

POLYPHARMACY

Polypharmacy has been defined in many ways. Some definitions focus on the number of medications, whereas others consider clinical appropriateness and indication.[10,14–16] Consequences to polypharmacy include the risk for clinically significant drug-drug interactions, adverse drug reactions, and nonadherence.[10]

Age is an important risk factor for polypharmacy.[14] Geriatric patients receiving multiple medications are at increased risk for cognitive impairment, falls, incontinence, and poor nutritional status.[10] The complex medical regimens of RA place older patients at such risks. Treharne and colleagues[17] found that the total number of RA medications was predicted by advancing age and longer disease duration. In addition, the total number of comorbidities contributed to this relationship. A 2001 study of hospitalized subjects with rheumatic diseases also found similar results, with older subjects having a higher likelihood of meeting the study's definition of polypharmacy compared with younger subjects.[18]

HEALTH LITERACY

Health literacy, defined as an individual's overall capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions, is another area where age-related changes may have an impact.[19] Wong and colleagues[20] noted that a third of patients prescribed common rheumatology medications followed the dosing instructions incorrectly. Several studies have found a relationship between older age and reduced health literacy. This relationship may be influenced by the educational level and age-related changes to functional status, such as visual impairment.[5,21–23] One study identified age older than 55 years as a risk factor for poor knowledge of MTX use in a diverse urban rheumatology clinic population in California.[24]

AGE BIAS

Older patients may face yet another challenge in receiving safe and effective treatment of rheumatologic disorders in the form of age bias, or disparities in the prescription of treatment by doctors based on patient age.[13,25,26] In a 2010 choice-based conjoint analysis, Kievit and colleagues[12] showed that among 135 rheumatologists, patient's age was an important factor in the decision to escalate RA treatment. Tutuncu and colleagues[27] found that patients with older-onset RA were less frequently treated with biologic drugs and combination DMARDs than those with younger-onset RA, even though they had comparable disease severity and activity. The reluctance to escalate therapy may result in older patients not receiving appropriate interventions, despite evidence of similar responsiveness to standard therapies when compared with younger patients.[28]

Because of these complexities, rheumatologists, working in partnership with other members of the allied health care team, can most effectively minimize the risk for therapeutic misadventure.

DISEASE-MODIFYING ANTIRHEUMATIC DRUGS AND THE RISK OF INFECTION

Autoimmune disease itself is a risk factor for infection. Patients with RA were found to have a higher risk of infection, when compared with control subjects with no RA.[29] Addition of immunosuppressive and immunomodulatory agents for the treatment of autoimmune disease further increase the risk of infection. In a systemic literature review of observational studies and RA registries, the risk of serious infections was

found to be higher among patients on biologic DMARDs compared with the conventional synthetic DMARDs, with a hazard ratio (HR) ranging from 1.1 to 2.4. The risk of tuberculosis was also significantly higher among patients on biologic DMARDS compared with the general population (HR, 34.9 [8.9–137.2]) and when compared with patients on conventional synthetic DMARDs (HR, 12.5 [3.5–44.7]).[30] As with other DMARDS, risk of infection is a concern with the targeted synthetic DMARD, tofacitinib. Pooled data from multiple phase 2, phase 3, and long-term extension studies of tofacitinib for RA found that the overall incidence rate of serious infections was 3 events per 100 patient-years. Pneumonia, herpes zoster, urinary tract infection, and cellulitis were the most common. The incidence rates were found comparable with other biologic DMARDs (3.0–5.5 per patient-years) and tumor necrosis factor (TNF) inhibitors (3.2–4.6 per patient-years). The incidence of infection did not increase with longer duration of tofacitinib use and was stable over time. The risk factors independently associated with increased risk of serious infection were age more than 65, corticosteroid use (>7.5 mg), diabetes, and tofacitinib dose.[31] Adequate vaccination of patients with rheumatologic disease is the key strategy in preventing infectious complications. Hence the Advisory Committee on Immunization Practices has recommended vaccination of patients with chronic inflammatory disease on immunosuppression with pneumococcal vaccines (PCV-13 followed by PCV-23) and annual influenza vaccine.[32]

METHOTREXATE

MTX is the most common DMARD used to treat RA and remains the cornerstone of treatment of this condition. The therapeutic effect of MTX in inflammatory arthritis was first reported in the 1950s,[33,34] but did not receive Food and Drug Administration (FDA) approval for the treatment of RA until 1988. It is also used to treat several other rheumatic conditions, such as juvenile idiopathic arthritis,[35,36] psoriatic arthritis,[37] reactive arthritis,[38] systemic lupus erythematosus (SLE),[39] granulomatosis with polyangiitis,[40] and polymyositis/dermatomyositis.[41]

The exact mechanism by which MTX exerts its therapeutic effects in RA is not fully understood. MTX is a folate analogue that enters the cells primary mediated by folate transporter 1, also known as reduced folate carrier 1. Once inside the cells, MTX undergoes polyglutamation catalyzed by folylpolyglutamate synthetase in the same manner as naturally occurring folate. MTX polyglutamates increase the retention of MTX in the cells and its inhibitory actions in several intracellular enzymes. First, MTX inhibits dihydrofolate reductase, the enzyme required for reduction of dihydrofolate (FH2) to tetrahydrolate (FH4), resulting in suppression of purines, thymidylate, serine, and methionine synthesis, and ultimately, DNA production. Second, MTX inhibits thymidylate synthetase, an enzyme that converts deoxyuridine monophosphate to deoxythymidine monophosphate, ultimately leading to decreased levels of pyrimidine that would be required for DNA biosynthesis. Finally, inhibition of 5-aminoimidazole-4-carboxamide ribonucleotide transformylase initiates a series of events that results in increased adenosine levels, which has multiple anti-inflammatory effects. For example, adenosine is associated with a decreased production of proinflammatory cytokines, such as TNF-α and interleukin (IL)-6, and increased production of anti-inflammatory cytokines, such as IL-10. It seems that adenosine, acting on adenosine receptors, is itself a key mediator of the anti-inflammatory effect of MTX, whereas the inhibition of dihydrofolate reductase and thymidylate synthetase seems to contribute more to antiproliferative effects.[42–44]

In the mid-1980s, four clinical trials in patients with active RA showed that MTX was superior to placebo in decreasing disease activity in the short-term.[45–48] Since then, MTX has been clearly established as a mainstay in the therapy for RA. A systematic review of seven randomized, placebo-controlled trials (n = 732 patients) in RA showed that MTX (doses between 5 mg and 25 mg weekly) was associated with a clinically important and statistically significant improvement in the American College of Rheumatology (ACR) 50 response rate at 52 weeks when compared with placebo (relative risk [RR], 3.0; 95% confidence interval [CI], 1.5–6.0). Radiographic progression rates were significantly lower in the MTX-treated group compared with the placebo group (RR, 0.31; 95% CI, 0.11–0.86) but no significant differences were observed in radiographic scores.[49] A 2016 network meta-analysis (158 trials, more than 37,000 patients) showed that the combination of MTX, SSZ, and HCQ (ie, triple therapy) was superior to MTX for ACR50 response and was not statistically different from MTX plus any biologic or tofacitinib in patients with no previous MTX use or with inadequate response to this medication.[50] The 2015 ACR guideline for the treatment of RA has recommended the use of MTX as a preferred initial DMARD for most patients with RA and to serve as the anchor drug in combination with biologic therapy.[51]

In rheumatic conditions, MTX is prescribed as a low-dose regimen (typically dosed $\leq$25 mg weekly). It is administered once weekly via oral, subcutaneous, or intramuscular route. There is no difference in the bioavailability of intramuscular versus subcutaneous route of administration,[52] but the former is not frequently used. Oral bioavailability varies broadly among patients and decreases with increasing dose. A phase 2 study that evaluated the relative bioavailability of oral versus subcutaneous MTX, showed that systemic exposure of oral MTX plateaued at doses greater than or equal to 15 mg weekly, whereas subcutaneous administration at the same dose resulted in linear increases in systemic exposure. Hence, subcutaneous injection at higher doses is an alternative approach that can improve bioavailability.[53] Another strategy to improve the bioavailability of oral administration includes splitting of the dose of MTX, such as giving one-half dose repeated 12 hours apart on the same day, once weekly. The efficacy of MTX dose splitting has only been addressed in limited studies.[54]

MTX is well tolerated in most patients with RA. In a 2014 systematic review of seven placebo-controlled trials, the adverse event rate at 12 weeks in the MTX monotherapy group was 45% (vs 15% in the placebo group; RR, 3.0; 95% CI, 1.4–6.4) and MTX was associated with a higher rate of discontinuation caused by adverse events compared with placebo (16% vs 8%; RR, 2.1; 95% CI, 1.3–3.3).[49] Another review of 21 prospective studies (2009) found that the long-term therapy (>2 years of treatment; n = 3463 patients) with MTX was associated with frequent adverse reactions (73%) but they were generally mild and caused discontinuation in around 11% of the patients.[55]

The most common adverse reactions of MTX are gastrointestinal (nausea, vomiting, abdominal pain, diarrhea, and stomatitis), elevated hepatic enzymes, dermatologic (skin rash, pruritus, and alopecia), neurologic (headache, vertigo, lethargy, and cognitive dysfunction), hematologic (cytopenia), and pulmonary (eg, pneumonitis). The rate of toxicity increases in patients with renal impairment.[56] MTX is eliminated primarily via renal excretion and may accumulate in the setting of reduced renal function.[57,58] Elevated liver enzymes are frequent adverse reactions and an important reason for treatment withdrawal. It occurs in up to 20% of patients and leads to discontinuation in 4% of patients during long-term use.[55] Although these events are usually self-limited, they can potentially lead to liver cirrhosis.[59] Risk factors for liver injury during

MTX therapy are alcohol use, history of liver disease (eg, hepatitis B or C), other comorbidities (diabetes, obesity, hyperlipidemia), exposure to hepatotoxic medications, lack of folate supplementation, persistent abnormal liver panel, and family history of heritable liver disease.[60]

Several measures are used to decrease adverse reactions associated with MTX. Laboratory monitoring for MTX toxicity should start with determining baseline complete blood cell counts, liver enzymes, and serum creatinine level; and thereafter followed by monitoring at regular intervals.[51] Folic acid or folinic acid supplementation may ameliorate some of the folate-pathway-dependent adverse effects, including hematologic, gastrointestinal, and hepatic side effects.[61] Switching from oral to parenteral route therapy or splitting the dose of MTX are other strategies that have been recommended albeit with limited scientific support.[62]

Few elderly patients were included in the initial trials with MTX but accumulating data over time has helped to better understand MTX in this population. The efficacy response of geriatric patients with active RA to MTX treatment is comparable with that of younger patients.[28] Given the safety profile of this medication, extra caution must be exercised when treating geriatric patients. A decline in renal function may be associated with impaired clearance and increased toxicity of MTX,[56–58] which is particularly relevant in the elderly. Close monitoring for signs of hepatic and hematologic toxicity should also be emphasized.

Elderly patients are vulnerable to clinically significant drug interactions with MTX. Trimethoprim-sulfamethoxazole (TMP-SMX), a commonly prescribed antibiotic with folate antagonist effect, can increase the occurrence of hematologic manifestations and life-threatening pancytopenia. In a 2010 systematic review of 67 articles addressing MTX-drug interactions,[63] cytopenia and elevation of liver enzymes were the main reported toxicities. In this review, clinically significant interactions with TMP-SMX therapy were noted in one observational study and in 17 case reports. TMP-SMX was mostly indicated for urinary tract infections. There were no reported cases of toxicity with use of prophylactic doses of three times per week. High-dose aspirin was also found to exacerbate the toxicity of MTX.[63] Other drugs known to cause hepatotoxicity, such as SSZ, leflunomide, and azathioprine, may increase the incidence of liver toxicity when used in combination with MTX.[64] Because MTX can accumulate in the setting of reduced clearance, medications that affect renal function should be avoided or used with caution (**Box 1**).

HYDROXYCHLOROQUINE

HCQ is another commonly used DMARD for the management of rheumatologic disorders. The precise mechanism of action of HCQ is unknown but is thought to have immunomodulatory and anti-inflammatory activity through stabilization of the lysosomal membrane, down-regulation of antigen presentation, and inhibition of cell-mediated cytotoxicity.[65] It also interferes with the innate immune response by inhibiting the Toll-like receptors.[66]

Box 1
Clinical pearls: MTX

- Monitor renal function; dose adjust accordingly.
- Folic acid or folinic acid supplementation can improve tolerability of MTX.
- Avoid concomitant use of TMP-SMX when dosed daily.

HCQ carries FDA approval for the treatment of RA and SLE. In RA, it is best used in mild, early disease or as a component of combination therapy. Treatment with HCQ was found to be an independent determinant of remission in RA in a multicenter cross-sectional study. HCQ has exhibited synergistic effects in improving disease activity when used in combination with other DMARDs, including MTX and SSZ (triple therapy).[67,68]

The use of HCQ is well established in cutaneous forms of SLE. In a comparative study of HCQ and acitretin, there was similar clinical efficacy, with 50% of the patients having a complete resolution of discoid lupus.[69] HCQ is beneficial in the management of non-organ-threatening disease manifestations including arthralgia, fatigue, fever, and rash. In patients with SLE, it has been demonstrated to decrease the risk of flare,[70] decrease the risk of thromboembolism in patients with antiphospholipid antibodies,[71] lower total cholesterol in patients taking steroids,[72] and lower fasting blood glucose concentration.[73] HCQ was also shown to have a beneficial effect on the survival of patients with lupus[74] and a protective effect on the risk of organ damage.[75]

HCQ is generally regarded as well tolerated, with gastrointestinal distress being the most common adverse effect. Skin hyperpigmentation is also a known side effect of long-term HCQ therapy. HCQ-induced blue-black dyschromia has been clinically misinterpreted as elder abuse. These cases were resolved after a thorough history or, in some cases, a skin biopsy.[76,77]

Postmarketing cases of cardiomyopathy and QT interval prolongation have been reported with the use of HCQ. Other rare adverse events reported include hypoglycemia, proximal myopathy, and neuropathy. For this reason, caution is recommended when coadministering with hypoglycemic agents or medications with arrhythmic potential.[78]

HCQ has the potential to cause irreversible retinal toxicity. A 2014 retrospective case-control study reviewed more than 2300 patient records of HCQ users with at least 5 years of treatment duration in a large integrated health organization of 3.4 million overall members. The overall prevalence of HCQ-related retinopathy was reported to be 7.5%, with risk dependent on dosage and duration of use. Patients on more than 5 mg/kg had 10% risk within 10 years of use and a 40% risk after 20 years of use. In patients using less than 5 mg/kg, the risk was reduced to 2% within the first 10 years and 20% after 20 years of use. Other risk factors for retinopathy include renal disease (glomerular filtration rate <60 mL/min) or concurrent use of tamoxifen. Notably, age was not identified as a risk factor.[79] Based on these data, the American Academy of Ophthalmology has recommended a maximum daily dosing of less than 5 mg/kg real body weight and a baseline fundus examination to rule out preexisting maculopathy. In patients with no major risk factors, the annual screening should be done after 5 years of HCQ use. The recommended modalities of screening are visual fields and spectral-domain optical coherence tomography (**Box 2**).[80]

Box 2
Clinical pearls: HCQ

- HCQ is a mainstay in the management of skin manifestations caused by SLE.
- Judicious dosing to avoid toxicity should be practiced using a 5.0 mg/kg actual body weight cutoff.
- Routine ophthalmology examinations are recommended to screen for the development of retinal toxicity.

SULFASALAZINE

SSZ is a well-established DMARD that is most commonly used as a second-line agent in RA combination therapy but is also indicated to treat other inflammatory arthritides and inflammatory bowel disease. SSZ is composed of sulfapyridine and 5-aminosalicylic acid and it is thought that the antiarthritic activity of this compound is mostly conferred by the sulfapyridine moiety. The precise mechanism of action of SSZ is not elucidated but may involve several anti-inflammatory and immunomodulatory effects, such as inhibition of proinflammatory cytokines (eg, TNF-α and IL-8) and increase of adenosine release at inflamed sites (similar to MTX).[81–83]

Genetic polymorphisms may play a role in the efficacy of the drug and the propensity for adverse effects. A prolonged half-life and accumulation of the sulfapyridine metabolite of SSZ with a subsequent increase in toxicity may be seen in slow acetylators.[84] Patients with glucose-6-phosphate dehydrogenase deficiency are at increased risk of hemolytic anemia after initiation SSZ treatment.[85]

Although it may be used alone, SSZ is typically prescribed with MTX and HCQ as part of so-called RA triple therapy. SSZ is the most commonly discontinued drug in this regimen secondary to adverse effects.[86] It is associated with gastrointestinal, central nervous system (headache, dizziness), cutaneous, and hematologic adverse reactions. The gastrointestinal complaints are usually mild in nature. They resolve with discontinuation or dose reduction and are better tolerated with the use of an enteric-coated formulation.[87,88]

A syndrome of fever, rash, and abnormal liver tests can occur in the setting of SSZ therapy. In the presence of eosinophilia, this reaction is termed drug rash with eosinophilia and systemic symptoms (DRESS syndrome).[89] Finally, a rare adverse effect of SSZ is crystalluria with intratubular precipitation of SSZ metabolites, and subsequent acute kidney injury.[90,91] Therefore, vigilance toward maintaining adequate hydration and monitoring renal function is prudent in older individuals treated with SSZ (**Box 3**).

LEFLUNOMIDE

Leflunomide is an isoxazole derivative that inhibits dihydroorotate dehydrogenase in the pyrimidine pathway. T lymphocytes are dependent on the de novo synthesis of pyrimidine. Decreased pyrimidine leads to decreased T-cell proliferation. Leflunomide is also known to modulate T-cell immunology by shifting the T-helper 1/T-helper 2 balance.[92] Consequently, it has successfully been used in the treatment of various inflammatory arthritides. It received FDA approval for use in RA in 1998. There are no large head-to-head randomized clinical trials comparing leflunomide with MTX, but the available evidence suggests a comparable clinical efficacy.[93] The use of leflunomide is limited by the lack of enough evidence for its use in combination with other biologic DMARDs.

Box 3
Clinical pearls: SSZ

- Initiation therapy with a gradual dose increase and interval laboratory monitoring can minimize the risk of adverse reactions.
- Slow acetylators and patients with glucose-6-phosphate dehydrogenase are at increased risk of toxicity.
- Crystalluria is a rare adverse effect. Patients should maintain adequate hydration.

Leflunomide has a similar safety profile as MTX. The most common reactions include gastrointestinal upset, hepatotoxicity, alopecia, and risk of infection.[93] Adverse events are similar regardless of patient age.[94] Safe prescribing of this agent relies on monitoring not only the blood count and liver function but also blood pressure. In a long-term study in patients with RA treated with leflunomide, clinically relevant increase in blood pressure was found in 5% of the patients but in most cases normalized during ongoing treatment.[95] Leflunomide is also associated with significant but modest weight loss compared to other RA medications.[96] In a small study of patients with RA treated with leflunomide, significant weight loss was found in 5 out of 70 patients (7%) and the weight loss ranged from 19 to 53 pounds (14%–26% decrease from baseline). Most patients had weight loss early (within 6 months) of initiation of the medication and on further continuation of medication the weight stabilized.[97] Hepatotoxicity is an important adverse reaction of leflunomide and cases of severe liver injury have been reported; therefore, it is not recommended to use in patients with preexisting liver disease.[98]

Because of low hepatic clearance and enterohepatic recycling, the pharmacokinetic profile of leflunomide is notable for a long elimination half-life of approximately 2 weeks.[99] In the setting of severe toxicity or other condition necessitating rapid withdrawal, cholestyramine is used to bind the active metabolite of leflunomide in the intestine and interrupt enterohepatic or enteroentero recycling, thus reducing the half-life to 1 to 2 days (**Box 4**).[99–102]

JANUS KINASE INHIBITORS

Janus kinase inhibitors are synthetic DMARDs that target the janus kinase (JAK) and signal transducer and activator of transcription (STAT) intracellular signaling pathway. The JAK/STAT pathway mediates intracellular signaling in a variety of ways. The JAK1-JAK3 complex is involved in lymphocyte proliferation induced by interleukins, such as IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21. The JAK 2 homodimer is essential in intracellular signaling by erythropoietin and granulocyte-macrophage colony–stimulating factor, which is required for erythropoiesis, myelopoiesis, and thrombopoiesis.[103] The JAK-STAT pathway is also involved in the host immune response against viral infection and mycobacterial infection.

Tofacitinib is a JAK inhibitor that is FDA approved for the treatment of RA. It inhibits JAK1 and JAK3, but also inhibits JAK 2 to a lesser degree.[104] It is indicated for the treatment of adult patients with moderate to severe RA with inadequate response or intolerance to MTX.[105–108] It may be used as monotherapy or in combination with MTX or other DMARDs. Tofacitinib is also approved for active psoriatic arthritis. Trials are currently underway studying the agent's effects in the management of other disease states, including juvenile idiopathic arthritis, SLE, psoriatic arthritis, and ankylosing spondylitis.

Box 4
Clinical pearls: leflunomide

- Hypertension and unintentional weight loss are two adverse effects related to leflunomide therapy that may be of particular concern in older patients.
- Regular monitoring for hepatotoxicity is recommended.
- In the clinical scenarios requiring rapid withdrawal of leflunomide, a cholestyramine washout is implemented to decrease the half-life of the active metabolite.

Tofacitinib is FDA-approved for daily dosing at 5 mg twice daily or with the extended-release formulation at 11 mg once daily. Tofacitinib is metabolized via cytochrome P-450 (CYP) 3A4 and a lesser degree via CYP2C19. Strong inhibitors of CYP 3A4 increase the effect of tofacitinib, increasing the toxicity, whereas inducers of CYP3A4 decrease the effect of tofacitinib (**Table 1**).

Herpes zoster infection is a concern in geriatric patients with RA on tofacitinib. Older age is one of the most important risk factors for the development of herpes zoster infection.[113] In addition, RA is an independent risk factor for herpes zoster (adjusted HR, 1.9 [95% CI, 1.8–2.0]).[114] In phase II, phase III, and long-term extension studies, the incidence rate of herpes zoster was found higher among the tofacitinib group compared with the placebo (crude incidence rate of 4.4 per 100 patient-years [95% CI, 3.8–4.9]) and was more common among Japanese and Korean patients. Not surprisingly, older age was associated with higher risk (odds ratio, 1.9; 95% CI, 1.5–2.6). Among the patients with herpes zoster, 7% of them had serious disease requiring hospitalization or use of intravenous antiviral treatment.[115] The risk of herpes zoster infection was found to be higher in patients taking tofacitinib in combination with glucocorticoids compared with those on monotherapy with only tofacitinib.[116] These studies underscore the importance of adequate vaccination before initiation of tofacitinib. The 2015 ACR guideline for the treatment of RA has recommended the administration of herpes zoster vaccine before starting biologic or tofacitinib in patients with RA age 50 years and older. After vaccination, they recommended a 2-week waiting period before starting a biologic.[51] The Infectious Disease Society of America has recommended administration of live vaccine greater than or equal to 4 weeks before the use of immunosuppressive agents.[117] Despite the safety and benefit of this approach, vaccination against herpes zoster is woefully underused in patients with RA.[118] A new recombinant zoster vaccine (Shingrex) was recommended by the Advisory Committee on Immunization Practices in 2017 for immunocompetent patients older than the age of 50 years. The vaccine is recommended at Day 0 with a repeat dose after 2 months.[119] This vaccine is found to be more efficacious and reduces the risk of herpes zoster and postherpetic neuralgia by more than 90%.[120] Because of the inactivated nature of the vaccine, it could be administered 2 weeks before the initiation of tofacitinib and this strategy could potentially mitigate the underuse of such vaccination.

Table 1
Clinically relevant medication interactions with tofacitinib

CYP Subset	Inhibitors	Inducers
CYP3A4	Clarithromycin Erythromycin Ketoconazole Itraconazole Diltiazem Verapamil Nelfinavir Ritonavir	Rifampin Phenytoin Carbamazepine
CYP2C19	Fluoxetine Fluvoxamine Isoniazid Ritonavir	Rifampicin Phenytoin Carbamazepine

Data from Refs.[109–112]

Winthrop and colleagues[121] illustrated a diminished responsiveness to the 23-valent pneumococcal polysaccharide vaccine (PPSV-23) in subjects commencing tofacitinib therapy at a dose of 10 mg twice daily. The response was further diminished in subjects with concomitant MTX. However, the response to annual influenza vaccination was unaltered in subjects receiving tofacitinib, with or without MTX. For current users, a 2-week holiday from tofacitinib around the time of vaccination did not appreciably improve immunogenicity for the PPSV-23 vaccine. Although most users developed sufficient responses to both vaccines, administration of the pneumococcal vaccine before initiation of tofacitinib may improve overall response and should be considered (**Box 5**).

APREMILAST

Apremilast is an oral small molecule that belongs to a class of new drugs known as phosphodiesterase-4 (PDE4) inhibitors. It was approved by the FDA for the treatment of psoriasis and psoriatic arthritis. PDE-4 is a superfamily of enzymes that catalyze the hydrolysis of cyclic adenosine monophosphate (cAMP).[122] Inhibition of PDE4 increases the levels of cAMP, a well-known intracellular second messenger that leads to activation of cAMP-dependent protein kinase A. This causes modifications of several transcription factors, such as the activation of cAMP-response element binding protein and inhibition of nuclear factor kappa B.[123,124] The specific mechanism of action by which apremilast exerts its therapeutic effects remains incompletely understood but it is known to modify the production of several cytokines, presumably enhancing cAMP actions at the transcriptional level. PDE4 inhibition reduces secretion of proinflammatory cytokines, such as TNF-α, interferon-γ, and IL-2; and increases production of anti-inflammatory modulators, such as IL-10.[125,126]

The efficacy and safety of apremilast for the treatment of psoriatic arthritis has been evaluated in four randomized, double-blinded, placebo-controlled phase 3 trials in the Psoriatic Arthritis Long-term Assessment of Clinical Efficacy programme (PALACE 1–4 trials).[127–131] Patients were randomized to receive apremilast, 20 or 30 mg twice daily, or placebo. PALACE 1 to 3 enrolled a total of 1493 patients with active psoriasis arthritis despite prior traditional DMARD or biologic treatment. PALACE 4 included 527 patients with no prior DMARD or biologic therapy. The primary end point was the ACR20 response rate at Week 16 and the key secondary endpoint was the change from baseline in the Health Assessment Questionnaire-Disability Index (HAQ-DI) score at Week 16. Apremilast improved signs and symptoms in patients with active psoriatic arthritis when compared with placebo. At Week 16, the ACR20 response rate was significantly higher with apremilast, 30 mg twice daily, than with placebo across all

Box 5
Clinical pearls: tofacitinib

- Tofacitinib is a new and effective treatment option for RA, which could be used with or without MTX.
- Patients should receive screening for tuberculosis before therapy initiation.
- Risk of infections including herpes zoster may be higher in patients receiving tofacitinib, specifically Asian patients.
- Tofacitinib therapy may blunt the immune response to specific vaccines; therefore, patients should be assessed for appropriate immunizations against herpes zoster, influenza, and pneumococcus before commencing therapy.

trials (40 vs 19% in PALACE 1, 32 vs 19% in PALACE 2, 41 vs 18% in PALACE 3, and 31 vs 16 in PALACE 4). Improvements in HAQ-DI were also seen with apremilast in PALACE trials. For example, in PALACE 1 the mean changes from baseline at Week 16 were −0.09 (standard error, 0.04) in the placebo group and −0.25 (0.04) in apremilast, 30 mg twice daily (P = .0015 vs placebo) in the per protocol population. Compared with placebo, a significantly greater proportion of patients receiving apremilast, 30 mg twice daily, achieved minimal clinically important differences of greater than or equal to 0.13 (39% placebo vs 50% apremilast, 30 mg twice daily; P = .0334) and greater than or equal to 0.30 (27% placebo vs 40% apremilast, 30 mg twice daily; P = .0149) as measured by the HAQ-DI at Week 16. This efficacy was sustained and the benefit of apremilast in psoriatic arthritis has been reported in extensions up to 4 years of treatment.[132]

The efficacy and safety of apremilast in active psoriatic arthritis was also evaluated in a phase 3B, randomized, double-blind, placebo-controlled trial (ACTIVE trial).[133] Patients (n = 219) who may have had one prior conventional therapy and were not previously treated with a biologic agent were randomized to apremilast, 30 mg twice daily (n = 110), or placebo (n = 109) for 24 weeks. A significantly greater ACR20 response at Week 16 (primary outcome) was observed with apremilast versus placebo (38% vs 20%; P = .004). This trial also assessed the onset of apremilast efficacy at earlier time points (beginning at Week 2) than in previous studies. At Week 2 (first assessment), response rates were 16% in apremilast group versus 6% (P = .025) in the placebo group. Improvements in other manifestations, including swollen and tender joints, enthesitis, physical impairment, and morning stiffness severity, were also observed with apremilast at Week 2. The benefit was maintained with continued treatment through Week 52.

Apremilast has an acceptable safety profile and, in general, is well tolerated. The most frequent adverse reactions are diarrhea, nausea, upper respiratory tract infection, and headache. The gastrointestinal manifestations are the most common reactions and typically are mild or moderate in severity, occur early in therapy, and resolve with continued treatment.[127–129] In the PALACE 1, the frequency of the most common adverse events reported with apremilast, 30 mg twice daily (n = 168), in the placebo-controlled phase (Weeks 0–24) were diarrhea (19.0%), nausea (18.5%), headache (10.7%), and upper respiratory tract infection (4.2%).[127] Weight loss has also been reported (5%–10% of body weight loss in 10%–12% of subjects; ≥10% of body weight loss in 2%). Therefore, it is recommended to monitor weight regularly in patients treated with apremilast, and consider discontinuation if unexplained or clinically significant weight loss occurs. Apremilast is also associated with an increase in reports of depression. Hence the risks and benefits of this medication should be weighed in patients with a history of depression or mood changes.[134] Treatment with apremilast is not associated with clinically meaningful laboratory abnormalities and routine laboratory monitoring is not required. However, baseline serum creatinine is important because the dose should be reduced to 30 mg once daily in patients with an estimated creatinine clearance less than 30 mL/min. In a pooled safety analysis of three trials (PALACE 1, 2, and 3), no new safety concerns were identified with long-term exposure over 52 weeks.[135]

The acceptable safety profile of apremilast makes this drug an appealing therapeutic option for geriatric patients. Of the total number of patients with psoriatic arthritis who enrolled in PALACE 1 to 3, around 10% (146 out of 1493) were 65 years of age or older. No overall differences were obtained in the safety profile of this age group compared with the younger group in the clinical studies. Similar results were obtained in the clinical trials of apremilast in psoriasis. In the Efficacy and Safety Trial Evaluating

Box 6
Clinical pearls: apremilast

- Apremilast has a favorable safety profile and is likely a viable therapeutic option for elderly patients with psoriatic arthritis.
- Evaluate risks of depression and monitor weight during therapy.
- Routine laboratory monitoring is not required during apremilast therapy.

the Effects of Apremilast in Psoriasis (ESTEEM 1 and 2) phase III clinical trial program,[136,137] about 9% (108 out of 1257) of the subjects who enrolled were 65 years of age or older. No overall differences were observed in the efficacy and safety in patients greater than or equal to 65 years of age and younger patients.[134]

The clinical use of apremilast has also been explored in other rheumatic and dermatologic conditions including RA, Behçet's disease, and different forms of dermatitis.[138] In RA, a phase 2, randomized, placebo-controlled trial in patients with active arthritis who had an inadequate response to MTX failed to meet the primary efficacy end point.[139] Further studies are needed to clarify the radiographic effect in psoriatic arthritis and to determine the actual therapeutic role compared with conventional DMARDs and biologics (**Box 6**).

SUMMARY

An effective treatment strategy targeting rheumatologic disorders in the elderly should be directed at maximizing the quality of life. In patients with RA, a treat-to-target approach with the goal of remission or low disease activity has improved outcomes.[140] However, treatment in geriatric patients is challenging because they are particularly vulnerable to adverse reactions. Factors known to increase this risk for adverse reactions include age-related changes in pharmacokinetics and pharmacodynamics, comorbidities, polypharmacy, and drug compliance issues. Moreover, pharmacotherapy in rheumatology is evolving rapidly, whereas guidance on how to apply the new advances to older individuals is frequently missing. Regular monitoring of clinical and laboratory parameters that is tailored to the specific medication and the comorbidities is crucial to minimize negative outcomes. Finally, educating the patient or caregiver and involving them in making decisions and setting the treatment goals is paramount to ensure an optimal outcome.

REFERENCES

1. Barbour KE, Helmick CG, Boring M, et al. Vital signs: prevalence of doctor-diagnosed arthritis and arthritis-attributable activity limitation—United States, 2013-2015. MMWR Morb Mortal Wkly Rep 2017;66(9):246–53.
2. Helmick CG, Felson DT, Lawrence RC, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part I. Arthritis Rheum 2008;58(1):15–25.
3. Choi HK, Hernan MA, Seeger JD, et al. Methotrexate and mortality in patients with rheumatoid arthritis: a prospective study. Lancet 2002;359(9313):1173–7.
4. Budnitz DS, Pollock DA, Weidenbach KN, et al. National surveillance of emergency department visits for outpatient adverse drug events. JAMA 2006; 296(15):1858–66.

5. Baker DW, Gazmararian JA, Sudano J, et al. The association between age and health literacy among elderly persons. J Gerontol B Psychol Sci Soc Sci 2000; 55(6):S368–74.
6. Joplin S, van der Zwan R, Joshua F, et al. Medication adherence in patients with rheumatoid arthritis: the effect of patient education, health literacy, and musculoskeletal ultrasound. Biomed Res Int 2015;2015:150658.
7. Turnheim K. When drug therapy gets old: pharmacokinetics and pharmacodynamics in the elderly. Exp Gerontol 2003;38(8):843–53.
8. Ranganath VK, Furst DE. Disease-modifying antirheumatic drug use in the elderly rheumatoid arthritis patient. Rheum Dis Clin North Am 2007;33(1): 197–217.
9. Shi S, Klotz U. Age-related changes in pharmacokinetics. Curr Drug Metab 2011;12(7):601–10.
10. Shah BM, Hajjar ER. Polypharmacy, adverse drug reactions, and geriatric syndromes. Clin Geriatr Med 2012;28(2):173–86.
11. Trifiro G, Spina E. Age-related changes in pharmacodynamics: focus on drugs acting on central nervous and cardiovascular systems. Curr Drug Metab 2011; 12(7):611–20.
12. Kievit W, van Hulst L, van Riel P, et al. Factors that influence rheumatologists' decisions to escalate care in rheumatoid arthritis: results from a choice-based conjoint analysis. Arthritis Care Res (Hoboken) 2010;62(6):842–7.
13. Juby A, Davis P. An evaluation of the impact of seniors on a rheumatology referral clinic: demographics and pharmacotherapy. Clin Rheumatol 2011; 30(11):1507–9.
14. Hovstadius B, Petersson G. Factors leading to excessive polypharmacy. Clin Geriatr Med 2012;28(2):159–72.
15. Hajjar ER, Cafiero AC, Hanlon JT. Polypharmacy in elderly patients. Am J Geriatr Pharmacother 2007;5(4):345–51.
16. Haider SI, Johnell K, Weitoft GR, et al. The influence of educational level on polypharmacy and inappropriate drug use: a register-based study of more than 600,000 older people. J Am Geriatr Soc 2009;57(1):62–9.
17. Treharne GJ, Douglas KM, Iwaszko J, et al. Polypharmacy among people with rheumatoid arthritis: the role of age, disease duration and comorbidity. Musculoskeletal Care 2007;5(4):175–90.
18. Viktil KK, Enstad M, Kutschera J, et al. Polypharmacy among patients admitted to hospital with rheumatic diseases. Pharm World Sci 2001;23(4):153–8.
19. Simonds SK. Health education as social policy. Health Educ Q 1974;2:1–10.
20. Wong PK, Christie L, Johnston J, et al. How well do patients understand written instructions?: health literacy assessment in rural and urban rheumatology outpatients. Medicine (Baltimore) 2014;93(25):e129.
21. Baker DW, Gazmararian JA, Williams MV, et al. Functional health literacy and the risk of hospital admission among Medicare managed care enrollees. Am J Public Health 2002;92(8):1278–83.
22. Buchbinder R, Hall S, Youd JM. Functional health literacy of patients with rheumatoid arthritis attending a community-based rheumatology practice. J Rheumatol 2006;33(5):879–86.
23. Caplan L, Wolfe F, Michaud K, et al. Strong association of health literacy with functional status among rheumatoid arthritis patients: a cross-sectional study. Arthritis Care Res (Hoboken) 2014;66(4):508–14.

24. Barton JL, Schmajuk G, Trupin L, et al. Poor knowledge of methotrexate associated with older age and limited English-language proficiency in a diverse rheumatoid arthritis cohort. Arthritis Res Ther 2013;15(5):R157.
25. Fraenkel L, Rabidou N, Dhar R. Are rheumatologists' treatment decisions influenced by patients' age? Rheumatology (Oxford) 2006;45(12):1555–7.
26. Radovits BJ, Fransen J, Eijsbouts A, et al. Missed opportunities in the treatment of elderly patients with rheumatoid arthritis. Rheumatology (Oxford) 2009;48(8):906–10.
27. Tutuncu Z, Reed G, Kremer J, et al. Do patients with older-onset rheumatoid arthritis receive less aggressive treatment? Ann Rheum Dis 2006;65(9):1226–9.
28. Koller MD, Aletaha D, Funovits J, et al. Response of elderly patients with rheumatoid arthritis to methotrexate or TNF inhibitors compared with younger patients. Rheumatology (Oxford) 2009;48(12):1575–80.
29. Doran MF, Crowson CS, Pond GR, et al. Frequency of infection in patients with rheumatoid arthritis compared with controls: a population-based study. Arthritis Rheum 2002;46(9):2287–93.
30. Ramiro S, Gaujoux-Viala C, Nam JL, et al. Safety of synthetic and biological DMARDs: a systematic literature review informing the 2013 update of the EULAR recommendations for management of rheumatoid arthritis. Ann Rheum Dis 2014;73(3):529–35.
31. Cohen S, Radominski SC, Gomez-Reino JJ, et al. Analysis of infections and all-cause mortality in phase II, phase III, and long-term extension studies of tofacitinib in patients with rheumatoid arthritis. Arthritis Rheumatol 2014;66(11):2924–37.
32. Available at: https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/immunocompetence.html. Accessed January 24, 2018.
33. Gubner R. Therapeutic suppression of tissue reactivity. I. Comparison of the effects of cortisone and aminopterin. Am J Med Sci 1951;221(2):169–75.
34. Gubner R, August S, Ginsberg V. Therapeutic suppression of tissue reactivity. II. Effect of aminopterin in rheumatoid arthritis and psoriasis. Am J Med Sci 1951;221(2):176–82.
35. Silverman E, Mouy R, Spiegel L, et al. Leflunomide or methotrexate for juvenile rheumatoid arthritis. N Engl J Med 2005;352(16):1655–66.
36. Ruperto N, Murray KJ, Gerloni V, et al. A randomized trial of parenteral methotrexate comparing an intermediate dose with a higher dose in children with juvenile idiopathic arthritis who failed to respond to standard doses of methotrexate. Arthritis Rheum 2004;50(7):2191–201.
37. Lie E, van der Heijde D, Uhlig T, et al. Effectiveness and retention rates of methotrexate in psoriatic arthritis in comparison with methotrexate-treated patients with rheumatoid arthritis. Ann Rheum Dis 2010;69(4):671–6.
38. Schmitt SK. Reactive arthritis. Infect Dis Clin North Am 2017;31(2):265–77.
39. Fortin PR, Abrahamowicz M, Ferland D, et al. Steroid-sparing effects of methotrexate in systemic lupus erythematosus: a double-blind, randomized, placebo-controlled trial. Arthritis Rheum 2008;59(12):1796–804.
40. De Groot K, Rasmussen N, Bacon PA, et al. Randomized trial of cyclophosphamide versus methotrexate for induction of remission in early systemic antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheum 2005;52(8):2461–9.
41. Fendler C, Braun J. Use of methotrexate in inflammatory myopathies. Clin Exp Rheumatol 2010;28(5 Suppl 61):S164–7.

42. Chabner BA, Allegra CJ, Curt GA, et al. Polyglutamation of methotrexate. Is methotrexate a prodrug? J Clin Invest 1985;76(3):907–12.
43. Chan ES, Cronstein BN. Molecular action of methotrexate in inflammatory diseases. Arthritis Res 2002;4(4):266–73.
44. Brown PM, Pratt AG, Isaacs JD. Mechanism of action of methotrexate in rheumatoid arthritis, and the search for biomarkers. Nat Rev Rheumatol 2016; 12(12):731–42.
45. Thompson RN, Watts C, Edelman J, et al. A controlled two-centre trial of parenteral methotrexate therapy for refractory rheumatoid arthritis. J Rheumatol 1984; 11(6):760–3.
46. Weinblatt ME, Coblyn JS, Fox DA, et al. Efficacy of low-dose methotrexate in rheumatoid arthritis. N Engl J Med 1985;312(13):818–22.
47. Williams HJ, Willkens RF, Samuelson CO Jr, et al. Comparison of low-dose oral pulse methotrexate and placebo in the treatment of rheumatoid arthritis. A controlled clinical trial. Arthritis Rheum 1985;28(7):721–30.
48. Andersen PA, West SG, O'Dell JR, et al. Weekly pulse methotrexate in rheumatoid arthritis. Clinical and immunologic effects in a randomized, double-blind study. Ann Intern Med 1985;103(4):489–96.
49. Lopez-Olivo MA, Siddhanamatha HR, Shea B, et al. Methotrexate for treating rheumatoid arthritis. Cochrane Database Syst Rev 2014;(6):CD000957.
50. Hazlewood GS, Barnabe C, Tomlinson G, et al. Methotrexate monotherapy and methotrexate combination therapy with traditional and biologic disease modifying antirheumatic drugs for rheumatoid arthritis: abridged Cochrane systematic review and network meta-analysis. BMJ 2016;353:i1777.
51. Singh JA, Saag KG, Bridges SL Jr, et al. 2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. Arthritis Rheumatol 2016;68(1):1–26.
52. Jundt JW, Browne BA, Fiocco GP, et al. A comparison of low dose methotrexate bioavailability: oral solution, oral tablet, subcutaneous and intramuscular dosing. J Rheumatol 1993;20(11):1845–9.
53. Schiff MH, Jaffe JS, Freundlich B. Head-to-head, randomised, crossover study of oral versus subcutaneous methotrexate in patients with rheumatoid arthritis: drug-exposure limitations of oral methotrexate at doses >/=15 mg may be overcome with subcutaneous administration. Ann Rheum Dis 2014;73(8):1549–51.
54. Dhaon P, Das SK, Srivastava R, et al. Oral methotrexate in split dose weekly versus oral or parenteral Methotrexate once weekly in rheumatoid arthritis: a short-term study. Int J Rheum Dis 2016. https://doi.org/10.1111/1756-185X.12910.
55. Salliot C, van der Heijde D. Long-term safety of methotrexate monotherapy in patients with rheumatoid arthritis: a systematic literature research. Ann Rheum Dis 2009;68(7):1100–4.
56. The effect of age and renal function on the efficacy and toxicity of methotrexate in rheumatoid arthritis. Rheumatoid Arthritis Clinical Trial Archive Group. J Rheumatol 1995;22(2):218–23.
57. Bressolle F, Bologna C, Kinowski JM, et al. Total and free methotrexate pharmacokinetics in elderly patients with rheumatoid arthritis. A comparison with young patients. J Rheumatol 1997;24(10):1903–9.
58. Bressolle F, Bologna C, Kinowski JM, et al. Effects of moderate renal insufficiency on pharmacokinetics of methotrexate in rheumatoid arthritis patients. Ann Rheum Dis 1998;57(2):110–3.

59. Wood PR, Caplan L. Drug-induced gastrointestinal and hepatic disease associated with biologics and nonbiologic disease-modifying antirheumatic drugs. Rheum Dis Clin North Am 2018;44(1):29–43.
60. Kalb RE, Strober B, Weinstein G, et al. Methotrexate and psoriasis: 2009 National Psoriasis Foundation Consensus Conference. J Am Acad Dermatol 2009;60(5):824–37.
61. Shea B, Swinden MV, Tanjong Ghogomu E, et al. Folic acid and folinic acid for reducing side effects in patients receiving methotrexate for rheumatoid arthritis. Cochrane Database Syst Rev 2013;(5):CD000951.
62. Katchamart W, Bourre-Tessier J, Donka T, et al. Canadian recommendations for use of methotrexate in patients with rheumatoid arthritis. J Rheumatol 2010; 37(7):1422–30.
63. Bourre-Tessier J, Haraoui B. Methotrexate drug interactions in the treatment of rheumatoid arthritis: a systematic review. J Rheumatol 2010;37(7):1416–21.
64. Anelli MG, Scioscia C, Grattagliano I, et al. Old and new antirheumatic drugs and the risk of hepatotoxicity. Ther Drug Monit 2012;34(6):622–8.
65. Fox R. Anti-malarial drugs: possible mechanisms of action in autoimmune disease and prospects for drug development. Lupus 1996;5(Suppl 1):S4–10.
66. Kuznik A, Bencina M, Svajger U, et al. Mechanism of endosomal TLR inhibition by antimalarial drugs and imidazoquinolines. J Immunol 2011;186(8):4794–804.
67. Moreland LW, O'Dell JR, Paulus HE, et al. A randomized comparative effectiveness study of oral triple therapy versus etanercept plus methotrexate in early aggressive rheumatoid arthritis: the treatment of early aggressive rheumatoid arthritis trial. Arthritis Rheum 2012;64(9):2824–35.
68. Wang GY, Zhang SL, Wang XR, et al. Remission of rheumatoid arthritis and potential determinants: a national multi-center cross-sectional survey. Clin Rheumatol 2015;34(2):221–30.
69. Jessop S, Whitelaw DA, Grainge MJ, et al. Drugs for discoid lupus erythematosus. Cochrane Database Syst Rev 2017;(5):CD002954.
70. Mok CC, Penn HJ, Chan KL, et al. Hydroxychloroquine serum concentrations and flares of systemic lupus erythematosus: a longitudinal cohort analysis. Arthritis Care Res (Hoboken) 2016;68(9):1295–302.
71. Petri M. Use of hydroxychloroquine to prevent thrombosis in systemic lupus erythematosus and in antiphospholipid antibody-positive patients. Curr Rheumatol Rep 2011;13(1):77–80.
72. Stojan G, Petri M. Atherosclerosis in systemic lupus erythematosus. J Cardiovasc Pharmacol 2013;62(3):255–62.
73. Chen YM, Lin CH, Lan TH, et al. Hydroxychloroquine reduces risk of incident diabetes mellitus in lupus patients in a dose-dependent manner: a population-based cohort study. Rheumatology (Oxford) 2015;54(7):1244–9.
74. Alarcon GS, McGwin G, Bertoli AM, et al, LUMINA Study Group. Effect of hydroxychloroquine on the survival of patients with systemic lupus erythematosus: data from LUMINA, a multiethnic US cohort (LUMINA L). Ann Rheum Dis 2007; 66(9):1168–72.
75. Akhavan PS, Su J, Lou W, et al. The early protective effect of hydroxychloroquine on the risk of cumulative damage in patients with systemic lupus erythematosus. J Rheumatol 2013;40(6):831–41.
76. Cohen PR. Hydroxychloroquine-associated hyperpigmentation mimicking elder abuse. Dermatol Ther (Heidelb) 2013;3(2):203–10.

77. True DG, Bryant LR, Harris MD, et al. Clinical images: hydroxychloroquine-associated mucocutaneous hyperpigmentation. Arthritis Rheum 2002;46(6):1698.
78. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/009768s037s045s047lbl.pdf. Accessed January 24, 2018.
79. Melles RB, Marmor MF. The risk of toxic retinopathy in patients on long-term hydroxychloroquine therapy. JAMA Ophthalmol 2014;132(12):1453–60.
80. Marmor MF, Kellner U, Lai TY, et al. Recommendations on screening for chloroquine and hydroxychloroquine retinopathy (2016 revision). Ophthalmology 2016;123(6):1386–94.
81. Rodenburg RJ, Ganga A, van Lent PL, et al. The antiinflammatory drug sulfasalazine inhibits tumor necrosis factor alpha expression in macrophages by inducing apoptosis. Arthritis Rheum 2000;43(9):1941–50.
82. Gadangi P, Longaker M, Naime D, et al. The anti-inflammatory mechanism of sulfasalazine is related to adenosine release at inflamed sites. J Immunol 1996;156(5):1937–41.
83. Volin MV, Campbell PL, Connors MA, et al. The effect of sulfasalazine on rheumatoid arthritic synovial tissue chemokine production. Exp Mol Pathol 2002;73(2):84–92.
84. Tarnowski M, Paradowska-Gorycka A, Dabrowska-Zamojcin E, et al. The effect of gene polymorphisms on patient responses to rheumatoid arthritis therapy. Expert Opin Drug Metab Toxicol 2016;12(1):41–55.
85. Mechanick JI. Coombs' positive hemolytic anemia following sulfasalazine therapy in ulcerative colitis: case reports, review, and discussion of pathogenesis. Mt Sinai J Med 1985;52(8):667–70.
86. Cummins L, Katikireddi VS, Shankaranarayana S, et al. Safety and retention of combination triple disease-modifying anti-rheumatic drugs in new-onset rheumatoid arthritis. Intern Med J 2015;45(12):1266–73.
87. Okubo S, Nakatani K, Nishiya K. Gastrointestinal symptoms associated with enteric-coated sulfasalazine (Azulfidine EN tablets). Mod Rheumatol 2002;12(3):226–9.
88. Weaver A, Chatwell R, Churchill M, et al. Improved gastrointestinal tolerance and patient preference of enteric-coated sulfasalazine versus uncoated sulfasalazine tablets in patients with rheumatoid arthritis. J Clin Rheumatol 1999;5(4):193–200.
89. Raithatha N, Mehrtens S, Mouyis M, et al. Rash and fever after sulfasalazine use. BMJ 2014;349:g5655.
90. DeMichele J, Rezaizadeh H, Goldstein JI. Sulfasalazine crystalluria-induced anuric renal failure. Clin Gastroenterol Hepatol 2012;10(2):A32.
91. Durando M, Tiu H, Kim JS. Sulfasalazine-induced crystalluria causing severe acute kidney injury. Am J Kidney Dis 2017;70(6):869–73.
92. Fragoso YD, Brooks JB. Leflunomide and teriflunomide: altering the metabolism of pyrimidines for the treatment of autoimmune diseases. Expert Rev Clin Pharmacol 2015;8(3):315–20.
93. Singer O, Gibofsky A. Methotrexate versus leflunomide in rheumatoid arthritis: what is new in 2011? Curr Opin Rheumatol 2011;23(3):288–92.
94. Alivernini S, Mazzotta D, Zoli A, et al. Leflunomide treatment in elderly patients with rheumatoid or psoriatic arthritis: retrospective analysis of safety and adherence to treatment. Drugs Aging 2009;26(5):395–402.

95. Kalden JR, Schattenkirchner M, Sorensen H, et al. The efficacy and safety of leflunomide in patients with active rheumatoid arthritis: a five-year followup study. Arthritis Rheum 2003;48(6):1513–20.
96. Baker JF, Sauer BC, Cannon GW, et al. Changes in body mass related to the initiation of disease-modifying therapies in rheumatoid arthritis. Arthritis Rheumatol 2016;68(8):1818–27.
97. Coblyn JS, Shadick N, Helfgott S. Leflunomide-associated weight loss in rheumatoid arthritis. Arthritis Rheum 2001;44(5):1048–51.
98. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020905s031lbl.pdf. Accessed January 24, 2018.
99. Rozman B. Clinical pharmacokinetics of leflunomide. Clin Pharmacokinet 2002;41(6):421–30.
100. Wong SP, Chu CM, Kan CH, et al. Successful treatment of leflunomide-induced acute pneumonitis with cholestyramine wash-out therapy. J Clin Rheumatol 2009;15(8):389–92.
101. Laub M, Fraser R, Kurche J, et al. Use of a cholestyramine washout in a patient with septic shock on leflunomide therapy: a case report and review of the literature. J Intensive Care Med 2016;31(6):412–4.
102. Hajdyla-Banas I, Banas T, Rydz-Stryszowska I, et al. Pregnancy course and neonatal outcome after exposure to leflunomide: 2 cases report and review of literature. Przegl Lek 2009;66(12):1069–71.
103. Winthrop KL. The emerging safety profile of JAK inhibitors in rheumatic disease. Nat Rev Rheumatol 2017;13(4):234–43.
104. Clark JD, Flanagan ME, Telliez JB. Discovery and development of Janus kinase (JAK) inhibitors for inflammatory diseases. J Med Chem 2014;57(12):5023–38.
105. Tanaka Y, Suzuki M, Nakamura H, et al. Phase II study of tofacitinib (CP-690,550) combined with methotrexate in patients with rheumatoid arthritis and an inadequate response to methotrexate. Arthritis Care Res (Hoboken) 2011;63(8):1150–8.
106. Fleischmann R, Kremer J, Cush J, et al. Placebo-controlled trial of tofacitinib monotherapy in rheumatoid arthritis. N Engl J Med 2012;367(6):495–507.
107. Fleischmann R, Cutolo M, Genovese MC, et al. Phase IIb dose-ranging study of the oral JAK inhibitor tofacitinib (CP-690,550) or adalimumab monotherapy versus placebo in patients with active rheumatoid arthritis with an inadequate response to disease-modifying antirheumatic drugs. Arthritis Rheum 2012;64(3):617–29.
108. Kremer JM, Cohen S, Wilkinson BE, et al. A phase IIb dose-ranging study of the oral JAK inhibitor tofacitinib (CP-690,550) versus placebo in combination with background methotrexate in patients with active rheumatoid arthritis and an inadequate response to methotrexate alone. Arthritis Rheum 2012;64(4):970–81.
109. Dresser GK, Spence JD, Bailey DG. Pharmacokinetic-pharmacodynamic consequences and clinical relevance of cytochrome P450 3A4 inhibition. Clin Pharmacokinet 2000;38(1):41–57.
110. Sager JE, Lutz JD, Foti RS, et al. Fluoxetine- and norfluoxetine-mediated complex drug-drug interactions: in vitro to in vivo correlation of effects on CYP2D6, CYP2C19, and CYP3A4. Clin Pharmacol Ther 2014;95(6):653–62.
111. Westphal JF. Macrolide-induced clinically relevant drug interactions with cytochrome P-450A (CYP) 3A4: an update focused on clarithromycin, azithromycin and dirithromycin. Br J Clin Pharmacol 2000;50(4):285–95.

112. Pelkonen O, Turpeinen M, Hakkola J, et al. Inhibition and induction of human cytochrome P450 enzymes: current status. Arch Toxicol 2008;82(10):667–715.
113. Insinga RP, Itzler RF, Pellissier JM, et al. The incidence of herpes zoster in a United States administrative database. J Gen Intern Med 2005;20(8):748–53.
114. Smitten AL, Choi HK, Hochberg MC, et al. The risk of herpes zoster in patients with rheumatoid arthritis in the United States and the United Kingdom. Arthritis Rheum 2007;57(8):1431–8.
115. Winthrop KL, Yamanaka H, Valdez H, et al. Herpes zoster and tofacitinib therapy in patients with rheumatoid arthritis. Arthritis Rheumatol 2014;66(10):2675–84.
116. Winthrop KL, Curtis JR, Lindsey S, et al. Herpes zoster and tofacitinib: clinical outcomes and risk of concomitant therapy. Arthritis Rheumatol 2017;69(10): 1960–8.
117. Rubin LG, Levin MJ, Ljungman P, et al. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. Clin Infect Dis 2014;58(3):309–18.
118. Zhang J, Delzell E, Xie F, et al. The use, safety, and effectiveness of herpes zoster vaccination in individuals with inflammatory and autoimmune diseases: a longitudinal observational study. Arthritis Res Ther 2011;13(5):R174.
119. Available at: https://www.fda.gov/downloads/.../Vaccines/ApprovedProducts/UCM581605.pdf. Accessed January 24, 2018.
120. Cunningham AL, Lal H, Kovac M, et al. Efficacy of the herpes zoster subunit vaccine in adults 70 years of age or older. N Engl J Med 2016;375(11):1019–32.
121. Winthrop KL, Silverfield J, Racewicz A, et al. The effect of tofacitinib on pneumococcal and influenza vaccine responses in rheumatoid arthritis. Ann Rheum Dis 2016;75(4):687–95.
122. Man HW, Schafer P, Wong LM, et al. Discovery of (S)-N-[2-[1-(3-ethoxy-4-methoxyphenyl)-2-methanesulfonylethyl]-1,3-dioxo-2,3-dihy dro-1H-isoindol-4-yl] acetamide (apremilast), a potent and orally active phosphodiesterase 4 and tumor necrosis factor-alpha inhibitor. J Med Chem 2009;52(6):1522–4.
123. Mayr B, Montminy M. Transcriptional regulation by the phosphorylation-dependent factor CREB. Nat Rev Mol Cell Biol 2001;2(8):599–609.
124. Ollivier V, Parry GC, Cobb RR, et al. Elevated cyclic AMP inhibits NF-kappaB-mediated transcription in human monocytic cells and endothelial cells. J Biol Chem 1996;271(34):20828–35.
125. Claveau D, Chen SL, O'Keefe S, et al. Preferential inhibition of T helper 1, but not T helper 2, cytokines in vitro by L-826,141 [4-[2-(3,4-Bisdifluromethoxyphenyl)-2-[4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan- 2-yl)-phenyl]-ethyl]3-methylpyridine-1-oxide], a potent and selective phosphodiesterase 4 inhibitor. J Pharmacol Exp Ther 2004;310(2):752–60.
126. Eigler A, Siegmund B, Emmerich U, et al. Anti-inflammatory activities of cAMP-elevating agents: enhancement of IL-10 synthesis and concurrent suppression of TNF production. J Leukoc Biol 1998;63(1):101–7.
127. Kavanaugh A, Mease PJ, Gomez-Reino JJ, et al. Treatment of psoriatic arthritis in a phase 3 randomised, placebo-controlled trial with apremilast, an oral phosphodiesterase 4 inhibitor. Ann Rheum Dis 2014;73(6):1020–6.
128. Cutolo M, Myerson GE, Fleischmann RM, et al. A phase III, randomized, controlled trial of apremilast in patients with psoriatic arthritis: results of the PALACE 2 trial. J Rheumatol 2016;43(9):1724–34.
129. Edwards CJ, Blanco FJ, Crowley J, et al. Apremilast, an oral phosphodiesterase 4 inhibitor, in patients with psoriatic arthritis and current skin involvement: a phase III, randomised, controlled trial (PALACE 3). Ann Rheum Dis 2016; 75(6):1065–73.

130. Wells A, Adebajo AO, Aelion JA, et al. Apremilast, an oral phosphodiesterase 4 inhibitor, is associated with long-term (52-week) improvement in the signs and symptoms of psoriatic arthritis in DMARD-naive patients: results from a phase 3, randomized, controlled trial. Arthritis Rheumatol 2014;66(Suppl 10):S680 [abstract: 1543].
131. Efficacy and Safety Study of Apremilast to Treat Active Psoriatic Arthritis (PsA) (PALACE4). ClinicalTrials.gov website. Identifier: NCT01307423. 2017. Available at: https://clinicaltrials.gov/ct2/show/results/NCT01307423. Accessed January 28, 2018.
132. Edwards CJ, Blanco FJ, Crowley JJ, et al. Apremilast is associated with long-term DAS-28 (CRP) remission and improvements in skin disease: results from a phase III study in DMARD/biologic-experienced active psoriatic arthritis patients. Arthritis Rheumatol 2016;68(Suppl 10) [abstract: 1734].
133. Nash P, Ohson K, Walsh J, et al. Early and sustained efficacy with apremilast monotherapy in biological-naive patients with psoriatic arthritis: a phase IIIB, randomised controlled trial (ACTIVE). Ann Rheum Dis 2018. https://doi.org/10.1136/annrheumdis-2017-211568.
134. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/206088s000lbl.pdf. Accessed January 14, 2018.
135. Mease PJ, Kavanaugh A, Gladman D, et al. Long-term safety and tolerability of apremilast, an oral phosphodiesterase 4 inhibitor, in patients with psoriatic arthritis: pooled safety analysis of three phase 3, randomized, controlled trials. Arthritis Rheumatol 2013;65(Suppl 10):S131 [abstract: 310].
136. Papp K, Reich K, Leonardi CL, et al. Apremilast, an oral phosphodiesterase 4 (PDE4) inhibitor, in patients with moderate to severe plaque psoriasis: results of a phase III, randomized, controlled trial (efficacy and safety trial evaluating the effects of apremilast in psoriasis [ESTEEM] 1). J Am Acad Dermatol 2015;73(1):37–49.
137. Paul C, Cather J, Gooderham M, et al. Efficacy and safety of apremilast, an oral phosphodiesterase 4 inhibitor, in patients with moderate-to-severe plaque psoriasis over 52 weeks: a phase III, randomized controlled trial (ESTEEM 2). Br J Dermatol 2015;173(6):1387–99.
138. Sakkas LI, Mavropoulos A, Bogdanos DP. Phosphodiesterase 4 inhibitors in immune-mediated diseases: mode of action, clinical applications, current and future perspectives. Curr Med Chem 2017;24(28):3054–67.
139. Genovese MC, Jarosova K, Cieslak D, et al. Apremilast in patients with active rheumatoid arthritis: a phase II, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. Arthritis Rheumatol 2015;67(7):1703–10.
140. Smolen JS, Breedveld FC, Burmester GR, et al. Treating rheumatoid arthritis to target: 2014 update of the recommendations of an international task force. Ann Rheum Dis 2016;75(1):3–15.

Sarcopenia
A Rheumatic Disease?

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KEYWORDS

• Sarcopenia • Muscle strength • Muscle atrophy • Frailty • Aging • Senescence
• Fall risk • Skeletal muscle mass loss

KEY POINTS

- Sarcopenia involves the loss of muscle mass, muscle strength, and physical function with aging.
- It is a prevalent but underrecognized problem in the elderly population, causing limitation of activities of daily living and increasing the risk of fall and mortality.
- To date, a common clinical definition and diagnostic criteria for sarcopenia are lacking. Many commonly used screening tools use parameters to assess for muscle mass, strength, and function to define sarcopenia.
- The goal of this article is to promote awareness among physicians of early recognition and management of sarcopenia.

INTRODUCTION

The term Sarcopenia (Greek, *sarx* for "flesh" and *penia* for "loss") refers to the phenomenon of reduction of muscular mass, strength, and function with aging.[1] Muscle strength is a critical component of walking, and its decrease in the elderly contributes to a high prevalence of falls. Sarcopenia is significantly associated with self-reported physical disability in both men and women, independent of ethnicity, age, morbidity, obesity, income, or health behaviors.[2] Reduced muscle strength with aging leads to loss of functional capacity and is a major cause of disability, mortality, and other adverse health outcomes.[3]

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As the number and proportion of elderly in the population continue to increase, sarcopenia-related morbidity will become an increasing area of health care resource utilization. Increased awareness of the condition among clinicians and researchers, especially rheumatologists, is paramount to recognize and manage this condition because early recognition and intervention can mitigate its deleterious outcomes. This review highlights the major aspects of sarcopenia, including definition, prevalence, pathophysiology, diagnosis, and management. The authors also discuss the causes and impact of secondary sarcopenia.

DEFINITION

Development of a universally applicable and acceptable definition of sarcopenia has been a major limitation in the advancement of the field. Since Rosenberg first coined the term sarcopenia in 1988,[1] multiple definitions of sarcopenia have been proposed, but to date there is no unanimously accepted method to define and diagnose sarcopenia. In 1998, Baumgartner and colleagues[2] proposed using lean skeletal muscle mass index (SMI) defined as appendicular (4 limbs) skeletal muscle mass as determined by dual X-ray absorptiometry (DEXA) divided by height (kg/m^2) and compared with a normal reference population as a standard measure for sarcopenia. This methodology showed promise. It is predictive for negative outcomes, and the same DEXA scan used in osteoporosis screening may be used to estimate the degree of sarcopenia, all with no added cost or radiation exposure to the patient.[2] However, muscle quantity or mass does not reflect quality and function of muscle.[4]

To account for these limitations, newer definitions of sarcopenia from the European Society on Clinician Nutrition and Metabolism special interest groups,[5] International Working Group on Sarcopenia (IWGS),[6] European Working Group on Sarcopenia in Older People (EWGSOP),[7] and the Foundation of the National Institute of Health (FNIH)[8] have proposed slightly differing definitions of sarcopenia that include muscle mass and function (**Table 1**). In addition, the EWGSOP suggested staging of sarcopenia into 3 different categories based on the presence of low muscle mass and the presence or absence of functional impairment[7] (**Table 2**). These progressive stages of sarcopenia have a dose-response relationship with functional limitations.

EPIDEMIOLOGY

There is a significant variability in the reported prevalence of sarcopenia due to differing definitions, tools of diagnosis, and patient populations. A recent study of community-dwelling older adults (average age of 67 years) in the United Kingdom found the prevalence of sarcopenia to be 4.6% in men and 7.9% in women using the EWGSOP criteria.[9] A study from the United States, conducted among adults with an average age of 70.1 years, reported the prevalence of sarcopenia to be as high as 36.5%.[10] In a Japanese population of community-dwelling elderly adults, the prevalence of sarcopenia ranged from 2.5% to 28.0% in men and 2.3% to 11.7% in women.[11]

Much of the difference in these estimates may be due to the lack of uniform criteria to diagnose sarcopenia. In fact, when assessing prevalence of sarcopenia in the same cohort using different definitions, it appears the FNIH criteria give a more conservative estimate (men = 1.3%, women = 2.3%), compared with IWGS (men = 5.1%, women = 11.8%) or EWGSOP criteria (men = 5.3%, women = 13.3%).[12] Interestingly, the criteria agreed in exclusion of sarcopenia but not for establishing a diagnosis. This differences underscores the critical need for a uniform, universally applicable operating definition of sarcopenia.

Table 1
Sarcopenia definitions from various consensus groups

Consensus Group	Muscle Mass	Muscle Strength	Physical Performance
ESPEN SIG[5]	>2 SD below mean muscle mass in adults 18–39 y old in NHANES III cohort	N/A	Gait speed <0.8 m/s
IWGS[6]	SMI • Men $\leq$7.23 kg/m^2 • Women $\leq$5.67 kg/m^2	N/A	Gait speed <1 m/s
EWGSOP[7]	SMI • Men $\leq$7.23 kg/m^2 • Women $\leq$5.67 kg/m^2	Hand grip strength • Men <30 kg • Women <20 kg	Gait speed <0.8 m/s
FNIH[8]	Muscle mass/BMI • Men $\leq$0.789 • Women $\leq$0.512	Hand grip strength • Men <26 kg • Women <16 kg	Gait speed <0.8 m/s

Abbreviations: BMI, body mass index; ESPEN SIG, European Society on Clinician Nutrition and Metabolism special interest groups; N/A, not applicable; NHANES III, 3rd National Health and Nutrition Examination Survey SMI,Skeletal Muscle Index as assessed by dual X-ray absorptiometry.

RISK FACTORS

Sarcopenia is considered by most to be an inevitable part of aging. However, the degree of sarcopenia is highly variable and depends on the presence of certain risk factors.

Lifestyle Lacking Exercise

Lack of exercise is thought to be the foremost risk factor for sarcopenia.[13] A gradual decline in muscle fiber numbers begins around 50 years of age.[14] Even professional athletes such as marathon runners and weight lifters show a gradual, albeit slower decline in their speed and strength with aging.[14] The decline in muscle fiber and strength is more pronounced in patients with sedentary lifestyle as compared with patients who are physically more active.

Hormone and Cytokine Imbalance

Age-related decreases in anabolic hormone concentrations, including growth hormone, testosterone, thyroid hormone, and insulin-like growth factor, lead to loss of muscle mass and strength. Extreme muscle loss often results from a combination of diminishing hormonal anabolic signals and promotion of catabolic signals mediated through proinflammatory cytokines, such as tumor necrosis factor alpha (TNF-α) and

Table 2
Sarcopenia staging

Stage	Muscle Mass	Muscle Strength	Performance
Presarcopenia	Low	Normal	Normal
Sarcopenia	Low	Low	Normal or low
Severe sarcopenia	Low	Low	Low

Reproduced from: Cruz-Jentoft AJ, Baeyens JP, Bauer JM, et al. Sarcopenia: European consensus on definition and diagnosis: report of the European Working Group on sarcopenia in older people. Age Aging 2010;39(4):414.

interleukin-6 (IL-6).[15] Elevated levels of both TNF-α and IL-6 have been shown to be present in skeletal muscles of older individuals.

Protein Synthesis and Regeneration

A decrease in the body's ability to synthesize protein, coupled with inadequate intake of calories and/or protein to sustain muscle mass, is common in sarcopenia. Oxidized proteins increase in skeletal muscle with aging and lead to a buildup of lipofuscin and cross-linked proteins that are inadequately removed via the proteolysis system. Which leads to an accumulation of noncontractile dysfunctional protein in skeletal muscles and is part of the reason muscle strength decreases severely in sarcopenia.[16]

Motor Unit Remodeling

Age-related reduction in motor nerve cells responsible for sending signals from the brain to the muscles to initiate movement also occurs. Satellite cells are small mononuclear cells that abut muscle fibers and are normally activated upon injury or exercise. In response to these signals, satellite cells differentiate and fuse into the muscle fiber, helping to maintain muscle function. One current hypothesis is that sarcopenia is caused, in part, by a failure in satellite cell activation.[15]

Evolutionary Basis

Evolutionary theories implicate the failure of the body to maintain muscle mass and function with aging on genes that govern these traits. This hypothesis suggests that genes suited for high levels of obligatory muscular effort required for survival in the Late Paleolithic epoch are ill matched to a modern lifestyle characterized by high levels of lifelong sedentary behavior.[17]

Early Developmental Influences

Epidemiologic research into the developmental origins of health and disease has shown that early environmental influences on growth and development may have long-term consequences for human health. Low birth weight, considered a marker of a poor early environment, is associated with reduced muscle mass and strength in adult life.[18] One study has shown that lower birth weight is associated with a significant decrease in muscle fiber score, suggesting that developmental influences on muscle morphology may explain the association between low birth weight and sarcopenia.[19]

SARCOPENIA HISTOPATHOLOGY

Early sarcopenia is characterized by a decrease in the size of muscle. Over time, a reduction in muscle tissue quality also occurs, which is characterized by replacement of muscle fibers with fat, an increase in fibrosis, changes in muscle metabolism, oxidative stress, and degeneration of the neuromuscular junction. These changes in the muscle ultimately leads to progressive loss of muscle function and to frailty.[15]

Studies looking at the histologic changes in muscle fibers reveal that sarcopenia predominantly affects the type II (fast-twitch) muscle fibers, whereas type I (slow-twitch) fibers are much less affected.[20] The size of type II fibers can be reduced by up to 50% in sarcopenia. However, such reductions are only moderate when compared with overall reductions in muscle mass, which raises the possibility that sarcopenia represents a reduction in muscle fiber number as well as reduced fiber size. Histologic studies comparing muscle cross-sections of elderly with those of younger individuals reveal at least 50% fewer type I and type II fibers by the ninth decade.[21]

Multiple factors have been implicated to contribute to these histologic changes, such as chronic neuropathy due to loss of anterior horn cells and ventral root fibers associated with aging,[22,23] lifestyle, hormones, inflammatory cytokines, and genetic factors.

SCREENING AND DIAGNOSIS

Although various consensus groups have different recommendations for screening, in general, elderly patients and/or patients with a history or recurrent falls, unintentional weight loss, or other chronic conditions such as heart disease should be assessed for impairment in their activities of daily living (ADLs). Those with impaired ADLs should undergo more specific testing for sarcopenia. Most consensus groups recommend initial testing of mobility impairment with gait speed that involves assessing time taken to walk 4 m at normal pace. If gait speed falls below 0.8 m/s (1 m/s under IWGS criterion), then assessment of muscle mass or strength should be performed. Other assessment of physical performance includes assessment of balance, climbing stairs, and rising from a chair.

Body composition can be assessed by DEXA, anthropometry, bioelectrical impedance, MRI, or CT scan. DEXA is the most widely accepted method of assessing appendicular muscle mass; however, it is limited by its inability to differentiate intramuscular fat or water.[24] Another method used to assess for muscle mass is bioimpedance analysis, which calculates electrical resistance using sensors to measure muscle mass, but has been shown to overestimate muscle mass and underestimate fat mass.[24,25]

Grip strength is the preferred and most widely used method to assess muscle strength. It involves using hydraulic dynamometer, whereby the participant is asked to squeeze as hard as they can for 3 seconds. The Process repeated three times on each side, alternating between left and right, and the highest reading is recorded. For patients with hand deformity, pain, or stiffness, a rubber-ball model dynamometer is more acceptable.

MANAGEMENT

Early recognition and intervention are keys to improved outcomes in patients with sarcopenia. Assessment of patients' environments for fall hazards and implementation of precautionary safety measures should be part of the treatment strategy.

Current Treatment Options

Resistance training exercise and vibration therapy

Physical inactivity is linked to loss of muscle strength and mass. Therefore, an exercise regimen is considered a cornerstone in the treatment of sarcopenia. Both resistance training and strength training of muscles are successful interventions in the prevention and treatment of sarcopenia by virtue of their positive influence on (1) the neuromuscular system, (2) an increase in anabolic hormone concentrations, and (3) an increase in the ability and capacity of the muscles to synthesize proteins.[26,27] Whole Body Vibration Therapy, which involves using specialized equipment with or without aerobic exercises, has also been reported to improve muscle strength and function.[28,29]

Nutritional supplementation

Malnutrition also contributes to sarcopenia. Nutritional screening and implementation of nutrition care plans similar to the approach to cachexia should be part of a

multidisciplinary approach to manage sarcopenia. A validated tool for nutritional needs assessment developed by The British Association for Parenteral and Enteral Nutrition is available online at www.bapen.org.uk.[30] Protein and amino acid supplementations like leucine-enriched whey protein in combination with resistance training have shown benefits to muscle mass, strength, and physical performance.[31–33] High-protein intake above the recommended daily allowance (in the range of 1.2–1.6 g/kg/d) has been suggested to prevent age-related sarcopenia.[34] Vitamin D supplementation (with or without whey protein) also appears to help improve muscle strength, especially in patients greater than 65 years and with a serum concentration less than 30 nmol/L.[32,35]

Pharmacologic Treatment Directions

Currently, there are no agents for the treatment of sarcopenia that have been approved by the US Food and Drug Administration. Anabolic agents to increase muscle building and agents that decrease muscle catabolism are being explored in sarcopenia.[36]

Androgen/androgen receptor modulators

Testosterone has been used as a therapeutic intervention for sarcopenia for many years. It has a positive effect on muscle mass; it increases muscle strength, and it improves functional measures such as gait speed. However, treatment with testosterone is limited because of adverse effects such as increased risk of prostate cancer in men, virilization in women, and an overall increased risk of cardiovascular events.[37–39] Selective androgen receptor modulators (SARMs) are of particular interest because of their tissue selectivity. It is hoped that androgenic signaling with these agents can achieve gains in skeletal muscle mass and strength without dose-limiting adverse events.[40,41] One agent, MT-102, has recently been tested in a phase 2 clinical study for treating cachexia in patients with late-stage cancer. The study data show significant increases in body weight in patients treated with 10 mg of MT-102 twice daily over the study period of 16 weeks, compared with a significant decrease in body weight in patients receiving placebo treatment.[42] Another SARM, MK-0773, showed increase in muscle mass; however, it did not show any difference in strength or function in women with sarcopenia.[43]

Myostatin inhibition

Myostatin is highly expressed in skeletal muscle cells and prevents muscle growth. Inhibitors targeting myostatin or its receptor (ActRIIB) have been developed to help improve muscle mass and strength. A humanized monoclonal antibody, LY2495655, has shown increase in muscle mass and improvement in functional measures of muscle power in elderly patients with increased falls in a phase 2 clinical trial.[44] Bimagrumab (BYM338) is an anti–myostatin receptor antibody that has shown promising results with increase in muscle mass, strength, and gait speed in a phase 2 clinical trial in patients with sarcopenia.[45] Further studies with these and other myostatin inhibitors are under way and will provide further information on their efficacy and safety.

Other therapies in development

Other compounds under investigation as treatments for sarcopenia include growth hormone, angiotensin-converting enzyme inhibitors, β1-antagonists like espindolol, eicosapentaenoic acid, thalidomide, OHR/AVR118 (a novel peptide-nucleic acid immunomodulator), celecoxib (COX-2 inhibitor), VT-122 (combination β-antagonist and COX-2 inhibitor), omega-3 supplements, and anabolic agents, such as ghrelin and its analogues, and ruxolotinib.[46]

Herbal supplements

There is a considerable interest in using herbal supplements in sarcopenia. A recent review reported a large number of herbal compounds with effects on skeletal muscles.[47] Some of the herbal compounds like curcumin from *Curcuma longa*, alkaloids and steroidal lactones from *Withania somnifera*, catechins from *Camellia sinensis*, proanthocyanidin of grape seeds, and gingerols and shogaols from *Zingiber officinale* showed modest effects on skeletal muscle in human studies.[47] However, the data supporting use of these supplements in people are limited with regards to efficacy, potential drug interactions, and adverse effects, and thus, recommendations for their use in sarcopenia are limited pending further research.

SECONDARY SARCOPENIA

Sarcopenia is often related to other underlying medical conditions. The pathogenic mechanisms that cause muscle wasting in secondary sarcopenia can provide useful insights into age-related sarcopenia. The management of secondary sarcopenia should focus on treating the underlying primary condition, with the same strategies to improve skeletal muscle strength and mass outlined previously.

Cachexia

Cachexia is characterized by severe muscle wasting usually accompanying severe systemic diseases, such as cancer, cardiomyopathy, and end-stage renal disease. Cachexia has recently been defined as a complex metabolic syndrome associated with underlying illness and characterized by loss of muscle with or without loss of fat mass.[48] Cachexia is frequently associated with inflammation, insulin resistance, anorexia, and increased breakdown of muscle proteins. Thus, most cachectic individuals are also sarcopenic, but most sarcopenic individuals are not considered cachectic. Sarcopenia is among the elements of the proposed definition for cachexia.[48]

Frailty

Frailty is a geriatric syndrome resulting from age-related cumulative declines across multiple physiologic systems, with impaired homeostatic reserve and a reduced capacity of the organism to withstand stress. The syndrome encompasses increased vulnerability to adverse health outcomes, such as falls, hospitalization, institutionalization, and mortality.[49] Frailty is based on readily identifiable physical impairments, with the presence of 3 or more of the following characteristics: unintended weight loss, exhaustion, weakness, slow gait speed, and low physical activity.[49,50] There exists significant overlap between frailty and sarcopenia; most frail older people have sarcopenia, which suggests a common pathogenic mechanism. The general concept of frailty, however, goes beyond physical factors to encompass psychological and social dimensions, such as cognitive decline, lack of social support, and the impact of the local environment.[50]

Sarcopenic Obesity

Sarcopenic obesity (SO) is a medical condition in which low lean body mass seen in sarcopenia is coupled with high fat mass. It is associated with impaired functional capacity, disability, metabolic complications, and mortality.[51] The reported prevalence of SO is between 2% and 21.7%. The likely explanation for wide variability in reported prevalence is due to factors such as lack of awareness of SO among health care providers and differences in genetics, nutrition, and lifestyle. In conditions such as

malignancy, lean body mass may be los,t whereas fat mass is preserved or increased.[51] Studies in patients with SO reveal that changes in muscle composition like marbling, or fat infiltration into muscle, lowers muscle quality and work performance thereby contributing to weakness.[52] Studies to understand the pathogenesis of SO have also observed certain age-related patterns of fat composition like an initial increase and then leveling off of fat mass as well as redistribution of fat from subcutaneous tissue to muscle and viscera that may play a role in development of SO.[52]

Sarcopenia in Systemic Autoimmune Diseases

Patients with systemic autoimmune diseases like systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), spondyloarthritides, and systemic sclerosis are especially predisposed to developing sarcopenia in light of the underlying proinflammatory state and the decrease in muscle use due to inactivity and pain. Nearly 10% of SLE patients have been reported to have sarcopenia.[53] Loss of muscle mass and function is 2 to 3 times more common in RA patients.[53–55] Patients with RA have also been reported to have more rapid decline in their hand grip strength, which is inversely related to the duration of their disease, regardless of their age.[56] Similarly, patients with spondyloarthritis and systemic sclerosis have been reported to have higher prevalence of sarcopenia.[57–59] Inflammatory burden of the disease and treatment may influence the prevalence and extent of sarcopenia and its limitation on ADLs. Early treatment and control of disease along with physical therapy focusing on resistance training may help in prevention of sarcopenia in these patients.

SUMMARY AND FUTURE DIRECTION

Sarcopenia is a growing global health concern. Sarcopenia has been reported to affect 5% to 13% of persons aged 60 to 70 years and up to 50% of people older than 80 years of age.[60] In 2000, the number of people at least 60 years old around the world was estimated to be 600 million. This population is expected to increase to 1.2 billion by 2025 and 2 billion by 2050. Even with a conservative estimate of prevalence, sarcopenia affects more than 50 million people today and will affect more than 200 million people in the next 40 years.

The diagnosis of sarcopenia can be difficult to affirm. The comprehensive measurements used in research are not always practical in health care settings and do not typically influence care planning. Exercise remains the intervention of choice for managing sarcopenia, but implementing an exercise program may be challenging for many reasons. The role of nutrition in preventing and treating sarcopenia is less clear. Although there is vigorous debate about what level of protein intake is optimal, ensuring adequate protein intake and replacing deficient nutrients and vitamins are recommended.

Future research should focus on exploring the biological pathways that lead to sarcopenia, along with the search for improved diagnostic biomarkers. Increased awareness among patients and health care providers, early screening, and a multidisciplinary approach to treatment are the best current practices to minimize the overall adverse impact of sarcopenia.

REFERENCES

1. Rosenberg IH. Sarcopenia: origins and clinical relevance. J Nutr 1997;127(5 Suppl):990S–1S.
2. Baumgartner RN, Koehler KM, Gallagher D, et al. Epidemiology of sarcopenia among the elderly in New Mexico. Am J Epidemiol 1998;147(8):755–63.

3. Roubenoff R. Origins and clinical relevance of sarcopenia. Can J Appl Physiol 2001;26(1):78–89.
4. Barbat-Artigas S, Rolland Y, Vellas B, et al. Muscle quantity is not synonymous with muscle quality. J Am Med Dir Assoc 2013;14(11):852.e1-7.
5. Muscaritoli M, Anker SD, Argiles J, et al. Consensus definition of sarcopenia, cachexia and pre-cachexia: joint document elaborated by Special Interest Groups (SIG) "cachexia-anorexia in chronic wasting diseases" and "nutrition in geriatrics". Clin Nutr 2010;29(2):154–9.
6. Fielding RA, Vellas B, Evans WJ, et al. Sarcopenia: an undiagnosed condition in older adults. Current consensus definition: prevalence, etiology, and consequences. International working group on sarcopenia. J Am Med Dir Assoc 2011;12(4):249–56.
7. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, et al. Sarcopenia: European consensus on definition and diagnosis: report of the European Working Group on sarcopenia in older people. Age Ageing 2010;39(4):412–23.
8. Studenski SA, Peters KW, Alley DE, et al. The FNIH sarcopenia project: rationale, study description, conference recommendations, and final estimates. J Gerontol A Biol Sci Med Sci 2014;69(5):547–58.
9. Patel HP, Syddall HE, Jameson K, et al. Prevalence of sarcopenia in community-dwelling older people in the UK using the European Working Group on Sarcopenia in Older People (EWGSOP) definition: findings from the Hertfordshire Cohort Study (HCS). Age Ageing 2013;42(3):378–84.
10. Brown JC, Harhay MO, Harhay MN. Sarcopenia and mortality among a population-based sample of community-dwelling older adults. J Cachexia Sarcopenia Muscle 2016;7(3):290–8.
11. Kim H, Hirano H, Edahiro A, et al. Sarcopenia: prevalence and associated factors based on different suggested definitions in community-dwelling older adults. Geriatr Gerontol Int 2016;16(Suppl 1):110–22.
12. Dam TT, Peters KW, Fragala M, et al. An evidence-based comparison of operational criteria for the presence of sarcopenia. J Gerontol A Biol Sci Med Sci 2014;69(5):584–90.
13. Abate M, Di Iorio A, Di Renzo D, et al. Frailty in the elderly: the physical dimension. Eura Medicophys 2007;43(3):407–15.
14. Faulkner JA, Larkin LM, Claflin DR, et al. Age-related changes in the structure and function of skeletal muscles. Clin Exp Pharmacol Physiol 2007;34(11):1091–6.
15. Ryall JG, Schertzer JD, Lynch GS. Cellular and molecular mechanisms underlying age-related skeletal muscle wasting and weakness. Biogerontology 2008;9(4):213–28.
16. Marcell TJ. Sarcopenia: causes, consequences, and preventions. J Gerontol A Biol Sci Med Sci 2003;58(10):M911–6.
17. Booth FW, Chakravarthy MV, Spangenburg EE. Exercise and gene expression: physiological regulation of the human genome through physical activity. J Physiol 2002;543(Pt 2):399–411.
18. Sayer AA, Syddall HE, Gilbody HJ, et al. Does sarcopenia originate in early life? Findings from the Hertfordshire cohort study. J Gerontol A Biol Sci Med Sci 2004;59(9):M930–4.
19. Patel HP, Jameson KA, Syddall HE, et al. Developmental influences, muscle morphology, and sarcopenia in community-dwelling older men. J Gerontol A Biol Sci Med Sci 2012;67(1):82–7.

20. Doherty TJ. Invited review: aging and sarcopenia. J Appl Physiol (1985) 2003; 95(4):1717–27.
21. Lexell J, Taylor CC, Sjostrom M. What is the cause of the ageing atrophy? Total number, size and proportion of different fiber types studied in whole vastus lateralis muscle from 15- to 83-year-old men. J Neurol Sci 1988;84(2–3):275–94.
22. Doherty TJ, Brown WF. Age-related changes in the twitch contractile properties of human thenar motor units. J Appl Physiol (1985) 1997;82(1):93–101.
23. Tomlinson BE, Irving D. The numbers of limb motor neurons in the human lumbosacral cord throughout life. J Neurol Sci 1977;34(2):213–9.
24. Beaudart C, McCloskey E, Bruyere O, et al. Sarcopenia in daily practice: assessment and management. BMC Geriatr 2016;16(1):170.
25. Kim M, Shinkai S, Murayama H, et al. Comparison of segmental multifrequency bioelectrical impedance analysis with dual-energy X-ray absorptiometry for the assessment of body composition in a community-dwelling older population. Geriatr Gerontol Int 2015;15(8):1013–22.
26. Valenzuela T. Efficacy of progressive resistance training interventions in older adults in nursing homes: a systematic review. J Am Med Dir Assoc 2012;13(5): 418–28.
27. Roth SM, Ferrell RF, Hurley BF. Strength training for the prevention and treatment of sarcopenia. J Nutr Health Aging 2000;4(3):143–55.
28. Wei N, Pang MY, Ng SS, et al. Optimal frequency/time combination of whole-body vibration training for improving muscle size and strength of people with age-related muscle loss (sarcopenia): a randomized controlled trial. Geriatr Gerontol Int 2017;17(10):1412–20.
29. Lau RW, Liao LR, Yu F, et al. The effects of whole body vibration therapy on bone mineral density and leg muscle strength in older adults: a systematic review and meta-analysis. Clin Rehabil 2011;25(11):975–88.
30. Relph WL. Addressing the nutritional needs of older patients. Nurs Older People 2016;28(3):16–9.
31. Denison HJ, Cooper C, Sayer AA, et al. Prevention and optimal management of sarcopenia: a review of combined exercise and nutrition interventions to improve muscle outcomes in older people. Clin Interv Aging 2015;10:859–69.
32. Bauer JM, Verlaan S, Bautmans I, et al. Effects of a vitamin D and leucine-enriched whey protein nutritional supplement on measures of sarcopenia in older adults, the PROVIDE study: a randomized, double-blind, placebo-controlled trial. J Am Med Dir Assoc 2015;16(9):740–7.
33. Cramer JT, Cruz-Jentoft AJ, Landi F, et al. Impacts of high-protein oral nutritional supplements among malnourished men and women with sarcopenia: a multicenter, randomized, double-blinded, controlled trial. J Am Med Dir Assoc 2016; 17(11):1044–55.
34. Phillips SM, Chevalier S, Leidy HJ. Protein "requirements" beyond the RDA: implications for optimizing health. Appl Physiol Nutr Metab 2016;41(5):565–72.
35. Beaudart C, Buckinx F, Rabenda V, et al. The effects of vitamin D on skeletal muscle strength, muscle mass, and muscle power: a systematic review and meta-analysis of randomized controlled trials. J Clin Endocrinol Metab 2014;99(11): 4336–45.
36. Molfino A, Amabile MI, Rossi Fanelli F, et al. Novel therapeutic options for cachexia and sarcopenia. Expert Opin Biol Ther 2016;16(10):1239–44.
37. Sakuma K, Yamaguchi A. Sarcopenia and age-related endocrine function. Int J Endocrinol 2012;2012:127362.

38. Wakabayashi H, Sakuma K. Comprehensive approach to sarcopenia treatment. Curr Clin Pharmacol 2014;9(2):171–80.
39. Haddad RM, Kennedy CC, Caples SM, et al. Testosterone and cardiovascular risk in men: a systematic review and meta-analysis of randomized placebo-controlled trials. Mayo Clin Proc 2007;82(1):29–39.
40. Johansen KL, Painter PL, Sakkas GK, et al. Effects of resistance exercise training and nandrolone decanoate on body composition and muscle function among patients who receive hemodialysis: a randomized, controlled trial. J Am Soc Nephrol 2006;17(8):2307–14.
41. Dalton JT, Barnette KG, Bohl CE, et al. The selective androgen receptor modulator GTx-024 (enobosarm) improves lean body mass and physical function in healthy elderly men and postmenopausal women: results of a double-blind, placebo-controlled phase II trial. J Cachexia Sarcopenia Muscle 2011;2(3):153–61.
42. Stewart Coats AJ, Srinivasan V, Surendran J, et al. The ACT-ONE trial, a multicentre, randomised, double-blind, placebo-controlled, dose-finding study of the anabolic/catabolic transforming agent, MT-102 in subjects with cachexia related to stage III and IV non-small cell lung cancer and colorectal cancer: study design. J Cachexia Sarcopenia Muscle 2011;2(4):201–7.
43. Papanicolaou DA, Ather SN, Zhu H, et al. A phase IIA randomized, placebo-controlled clinical trial to study the efficacy and safety of the selective androgen receptor modulator (SARM), MK-0773 in female participants with sarcopenia. J Nutr Health Aging 2013;17(6):533–43.
44. Becker C, Lord SR, Studenski SA, et al. Myostatin antibody (LY2495655) in older weak fallers: a proof-of-concept, randomised, phase 2 trial. Lancet Diabetes Endocrinol 2015;3(12):948–57.
45. Rooks D, Praestgaard J, Hariry S, et al. Treatment of Sarcopenia with Bimagrumab: results from a phase II, randomized, controlled, proof-of-concept study. J Am Geriatr Soc 2017;65(9):1988–95.
46. Dingemans AM, de Vos-Geelen J, Langen R, et al. Phase II drugs that are currently in development for the treatment of cachexia. Expert Opin Investig Drugs 2014;23(12):1655–69.
47. Rondanelli M, Miccono A, Peroni G, et al. A systematic review on the effects of botanicals on skeletal muscle health in order to prevent sarcopenia. Evid Based Complement Alternat Med 2016;2016:5970367.
48. Evans WJ, Morley JE, Argiles J, et al. Cachexia: a new definition. Clin Nutr 2008; 27(6):793–9.
49. Bauer JM, Kaiser MJ, Sieber CC. Sarcopenia in nursing home residents. J Am Med Dir Assoc 2008;9(8):545–51.
50. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci 2001;56(3):M146–56.
51. Prado CM, Lieffers JR, McCargar LJ, et al. Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. Lancet Oncol 2008;9(7):629–35.
52. Ding J, Kritchevsky SB, Newman AB, et al. Effects of birth cohort and age on body composition in a sample of community-based elderly. Am J Clin Nutr 2007;85(2):405–10.
53. Santos MJ, Vinagre F, Canas da Silva J, et al. Body composition phenotypes in systemic lupus erythematosus and rheumatoid arthritis: a comparative study of Caucasian female patients. Clin Exp Rheumatol 2011;29(3):470–6.

54. Dao HH, Do QT, Sakamoto J. Abnormal body composition phenotypes in Vietnamese women with early rheumatoid arthritis. Rheumatology (Oxford) 2011; 50(7):1250–8.
55. Giles JT, Ling SM, Ferrucci L, et al. Abnormal body composition phenotypes in older rheumatoid arthritis patients: association with disease characteristics and pharmacotherapies. Arthritis Rheum 2008;59(6):807–15.
56. Beenakker KG, Ling CH, Meskers CG, et al. Patterns of muscle strength loss with age in the general population and patients with a chronic inflammatory state. Ageing Res Rev 2010;9(4):431–6.
57. Aguiar R, Sequeira J, Meirinhos T, et al. SARCOSPA - sarcopenia in spondyloarthritis patients. Acta Reumatol Port 2014;39(4):322–6.
58. El Maghraoui A, Ebo'o FB, Sadni S, et al. Is there a relation between presarcopenia, sarcopenia, cachexia and osteoporosis in patients with ankylosing spondylitis? BMC Musculoskelet Disord 2016;17:268.
59. Caimmi C, Caramaschi P, Venturini A, et al. Malnutrition and sarcopenia in a large cohort of patients with systemic sclerosis. Clin Rheumatol 2018;37(4):987–97.
60. Morley JE. Sarcopenia: diagnosis and treatment. J Nutr Health Aging 2008;12(7): 452–6.

The Relationship Between Rheumatologic Disorders and Malignancies

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KEYWORDS

• Musculoskeletal • Malignancy • Mimics • Paraneoplastic • Lymphoma
• Pitting edema • Fasciitis • Autoimmune

KEY POINTS

- Autoimmune conditions and their treatments may be associated with an increased risk of certain malignancies.
- The lack of response to conventional treatment of a rheumatic syndrome (eg, polymyalgia rheumatica [PMR] or inflammatory polyarthritis) should increase the suspicion for a paraneoplastic cause.
- Conditions such as palmar fasciitis with polyarthritis, hypertrophic osteoarthropathy, multicentric reticulohistiocytosis, and dermatomyositis have well-documented evidence for association with underlying malignancy.
- A higher incidence of non-Hodgkin lymphoma and other hematologic and lymphoproliferative diseases is seen in patients with primary Sjögren syndrome, systemic sclerosis, rheumatoid arthritis, and lupus, among others.

INTRODUCTION

Kankeleit[1] noted one of the earliest associations between cancer and polymyositis in 1916. Since then, a variety of clinical and epidemiologic associations between musculoskeletal symptoms and underlying malignancies have been described. However, determining causality between these conditions and malignancy remains challenging.

Certain malignancies occur with higher incidence in patients with autoimmune disorders. Mechanistically, this may relate to malignant transformation that can occur as a result of immune dysregulation in the later phase of certain autoimmune conditions. For example, non-Hodgkin lymphomas (NHLs) are reported with higher frequency in

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patients with primary Sjögren syndrome, rheumatoid arthritis (RA), and possibly in systemic lupus erythematosus (SLE).[2]

Many clinical presentations mimic rheumatologic conditions, which, in reality, are direct signs of the musculoskeletal spread of the underlying cancer or a paraneoplastic syndrome associated with it. These paraneoplastic rheumatic syndromes are not directly caused by local or distant spread of the tumor but are actually induced through a complex interaction of humoral and cytotoxic immune mechanisms, autocrine and paracrine mediators, and signaling pathways.

Certain conditions, such as hypertrophic osteoarthropathy (HOA), dermatomyositis, and palmar fasciitis with polyarthritis, have well-documented associations with cancer. However, a growing body of literature describes other conditions, including but not limited to remitting seronegative symmetric synovitis with pitting edema (RS3PE), carcinogenic polyarthritis, multicentric reticulohistiocytosis (MRH), leukocytoclastic vasculitis (LCV), scleroderma and the scleroderma mimics, eosinophilic fasciitis, and erythromelalgia.

It is difficult at times to discern association from coincidence because some of these associations are merely based on case reports or small series. Another limitation is that some reports are subject to a Berkson's bias, which occurs when patients but not controls are drawn from a hospital referral population. In this situation, the possibility of recognition of a hospitalized patient with both a primary rheumatic disorder and malignancy is much higher than for a patient with a rheumatic disorder alone. Finally, some reported associations are based on standardized incidence ratios (SIRs) and odds ratios, which reflect correlation between 2 disorders and not necessarily causality.[3]

In 1965, Sir Austin Bradford Hill[4] proposed criteria to guide establishing an argument for causation. These criteria may be used to determine if a given rheumatic condition can be attributed to the presence of an underlying malignancy. The summary of the Bradford Hill criteria is as follows: strength of association between the causative agent and the outcome, temporal sequence of the 2 conditions, consistency of results even when different methodology is used, theoretic plausibility, coherence (ie, whether or not the association makes theoretic sense), specificity in the causes, dose-response relationship, experimental evidence, and similar evidence from analogous conditions.[5]

The emphasis of this article is to increase awareness of those musculoskeletal conditions that should alert the clinician to a search for an occult malignancy. However, a comprehensive review of the primary and metastatic tumors of the musculoskeletal system is beyond the scope of this report.

CLINICAL CLUES FOR PRESENCE OF AN OCCULT MALIGNANCY

Several features can increase suspicion for the presence of an occult malignancy in an older patient with musculoskeletal complaints. Some of these include personal or family history of malignancy, prior exposure to carcinogenic medications or environmental pollutants, constitutional symptoms, unusual clinical picture for the rheumatic syndrome, and atypical or no response to conventional therapy.

There are other alarming presentations that may also trigger more intense search for occult malignancy, such as sudden-onset asymmetric polyarthritis presenting in the elderly, RA with monoclonal gammopathy, Sjögren syndrome with increasing globulin-albumin gap, HOA, dermatomyositis, PMR unresponsive to prednisone therapy, eosinophilic fasciitis poorly responsive to corticosteroid therapy, erythema nodosum lasting more than 6 months, and the new onset of Raynaud phenomenon or cutaneous LCV after age 50 years.[6]

SPECTRUM OF RHEUMATOLOGIC MANIFESTATIONS OF MALIGNANCIES

The musculoskeletal manifestations of malignancy can be caused by several underlying conditions. Symptoms may result from involvement of the bone, joint, muscles, or associated structures by the primary or metastatic tumors. Also, some specific autoimmune rheumatologic conditions are inherently associated with increased risk of malignancies. In addition, a variety of other factors, such as altered immune responses from treatment with immunosuppressive and antineoplastic medications, can contribute to development of rheumatologic manifestations in patients with cancer.

Primary or Metastatic Tumors Involving the Bone, Joint, Muscles, or Associated Structures

Musculoskeletal structures, including bones, articular cartilage, and synovium, as well as muscles and other periarticular structures, can become directly involved by a variety of neoplastic conditions. Primary malignant bone tumors, although uncommon, can cause significant cancer-related morbidity and mortality, particularly among younger people. Approximately 3300 primary malignant bone tumors are diagnosed annually in the United States, resulting in 1490 deaths each year. This does not include the extensive bone involvement that can be seen with hematologic malignancies such as multiple myeloma, leukemia, and lymphomas. The cumulative annual incidence for these latter neoplasms is approximately 172,000 cases in the United States alone.[7]

The World Health Organization's[8] "WHO Classification of Tumours of Soft Tissue and Bone," published in 2013, categorizes these tumors based on the tissue of origin, regardless of the malignant or benign nature of the tumor. The categories described in this classification include chondrogenic, osteogenic, fibrogenic, and fibrohistiocytic tumors, as well as Ewing sarcoma, hematopoietic neoplasms, osteoclastic giant cell–rich tumors, notochordal, vascular, myogenic, lipogenic, and epithelial tumors, tumors of undefined neoplastic nature, and undifferentiated high-grade pleomorphic sarcomas. Some tumors have a predilection for certain joints. As an example, pigmented villonodular synovitis, synovial hemangioma, synovial osteochondromatosis, and lipomatosis arborescens are a few of the benign tumors occurring in larger joints such as the knees. Examples of primary malignant intraarticular knee lesions include synovial sarcoma and synovial chondrosarcoma.

Certain cancers, such as lung, breast, and prostate, have a tendency to metastasize to bone. Breast cancer metastases are usually osteolytic with some reactive osteoblastic activity, whereas prostate cancer metastatic lesions are usually osteoblastic, presenting with elevated alkaline phosphatase and osteocalcin bone turnover markers.[9] Several other malignancies can spread to the bone. These metastatic lesions may be categorized as primarily osteolytic (eg, renal cell carcinoma, multiple myeloma, thyroid, non–small cell lung cancers, NHL, and melanoma), primarily osteoblastic (eg, prostate, small cell lung cancer, carcinoid, Hodgkin lymphoma, and medulloblastoma), and malignancies with both osteolytic and osteoblastic components (eg, breast, gastrointestinal, and squamous cell carcinomas). Malignant lesions involving the bones can be associated with significant pain and complications such as pathologic fracture, hypercalcemia, and spinal cord compression.

Increased Risk of Malignancies in Certain Autoimmune Rheumatologic Conditions

The increased incidence of malignancies in certain autoimmune rheumatic disorders has long been recognized. These may include chronic rheumatic syndromes such as RA, Felty syndrome (FS), Sjögren syndrome, dermatomyositis, systemic sclerosis, SLE, and systemic vasculitis. However, tumor markers such as α-fetoprotein,

prostate-specific antigen, CA-125, CA 19-9, and CA-3 have low sensitivity and specificity in screening for occult cancer in these patients. On the other hand, the presence of a monoclonal gammopathy in RA and the finding of monoclonal antibody 17-9 in Sjögren syndrome have been described as potential signs of malignant transformation.[6]

Rheumatoid arthritis

The association of malignancies with RA is somewhat controversial. An increased incidence of leukemias and lymphomas in RA has been well-recognized since 1978,[10] with the SIR for these cancers estimated to be between 1.9 and 2.7 in various studies.[11] Notably, colorectal malignancies are consistently reported to have a lower incidence in RA cohorts.[12] This observation has been made across several studies and is thought to be in part caused by the protective effects of the nonsteroidal anti-inflammatory drugs used in the adjunct therapy for these conditions.[13]

T-cell large granular lymphocyte leukemia (T-LGL) may be seen in the setting of chronic inflammation, neutropenia, and RA, and is characterized by clonal expansion of cytotoxic T cells. A subset of patients with FS demonstrates polyclonal expansion of LGLs. The polyclonality characteristic of FS helps distinguish it from T-LGL, which is associated with monoclonal LGL expansion. Despite this fundamental difference, T-LGL and FS may have clinical similarities. Both follow a chronic inflammatory course and both respond to immunosuppressive therapy.[14] RA can precede or occur concurrently with T-LGL leukemia. The arthritis in this setting may range from mild or intermittent to severe and deforming. Patients with concomitant RA and T-LGL leukemia frequently have antinuclear antibodies and may also occasionally have positive anti-cyclic citrullinated peptide antibody and rheumatoid factor.[15]

Systemic lupus erythematosus

An increased incidence of malignancies has also been noted in patients with SLE. The most consistent association exists between SLE and NHLs, which is estimated to encompass 3 to 4 times higher risk than in the general population. This association has been shown across several different population cohorts.[16] Additionally, some studies suggest an increased risk of other malignancies, such as lung and hepatobiliary cancers in SLE patients. As an example, a multicenter (23 sites) international cohort of 9547 subjects with SLE was observed for a total of 76,948 patient-years, with an average follow-up of 8 years. During the course of the study, 431 cancers occurred. For all cancers combined the SIR estimate was 1.15 (95% CI 1.05–1.27). For all hematologic malignancies the SIR was 2.75 (95% CI 2.13–3.49), and for NHL the SIR was 3.64 (95% CI 2.63–4.93). The data also suggested an increased risk of lung cancer (SIR 1.37, 95% CI 1.05–1.76) and hepatobiliary cancer (SIR 2.60, 95% CI 1.25–4.78).[17]

The same investigators published a follow-up article in 2013. This time the study was done in 30 centers and included 16,409 SLE subjects. The subjects were observed for 121,283 (average 7.4) person-years. In total, 644 cancers occurred. Some cancers, notably hematologic malignancies, were substantially increased (SIR 3.02, 95% CI 2.48, 3.63), particularly NHL (SIR 4.39, 95% CI 3.46–5.49) and leukemia. In addition, there was a significant increased risk of cancer of the vulva (SIR 3.78, 95% CI 1.52–7.78) and a modest increased risk of other malignancies such as lung (SIR 1.30, 95% CI 1.04–1.60), thyroid (SIR 1.76, 95% CI 1.13–2.61), and possibly liver (SIR 1.87, 95% CI 0.97–3.27). Interestingly, in this study, decreased risk for breast (SIR 0.73, 95% CI 0.61–0.88), endometrial (SIR 0.44, 95% CI 0.23–0.77), and possibly ovarian cancers (SIR 0.64, 95% CI 0.34–1.10) was observed. The variability of

comparative rates across different cancers statistically translates into only a small increased risk across all cancers (SIR 1.14, 95% CI 1.05–1.23). The investigators could not draw a conclusion concerning the mechanism of the positive association between SLE and NHL. Similarly, the reason for the observed decreased breast, endometrial, and possibly ovarian cancer risk remains to be elucidated.[18]

A Swedish study that included 6438 SLE subjects noted that the overall 5-year survival rate (50%) and mean age (61 years) for SLE subjects with NHL was comparable with those for NHL in the general population. However, the more aggressive NHL subtype of diffuse large B cell lymphoma was reported more frequently in the lupus cohort. This association was independent of history of treatment with cyclophosphamide or azathioprine. Conversely, the NHL risk was higher in patients with hematologic aberrations, sicca symptoms, or pulmonary involvement.[19]

Finally, a recent US population-based cohort study of 133,333 subjects with systemic inflammatory disease (SID), which included 58,979 RA subjects and 14,513 SLE subjects, compared the crude incidence rate of high-grade cervical dysplasia and cervical cancer per 100,000 person-years with a control group of 533,332 subjects without SID. They followed up with the subjects for 2 years. The risk of high-grade cervical dysplasia and cervical cancer was 1.5 times higher in women with RA and SLE than in those without SID.[20]

Systemic sclerosis and myositis

The most commonly associated malignancy in patients with systemic sclerosis is lung cancer. Smoking is an important risk factor. In an Australian study, scleroderma subjects who smoked were 7 times more likely to subsequently develop lung cancer than nonsmokers ($P = .008$). Pulmonary fibrosis and antitopoisomerase antibody did not increase the risk of lung cancer.[21] However, a close temporal relationship between the onset of cancer and scleroderma in patients with antibodies to RNA polymerase I or III has been noted. Malignancy may initiate the scleroderma-specific immune response and drive the disease in a subset of scleroderma patients.[22] The risk of other malignancies, such as esophageal and oropharyngeal malignancies, is also increased.[23] Several scleroderma-like dermatoses, such as scleromyxedema and scleredema, have also been reported in association with paraproteinemia.

Inflammatory myopathies

The association between dermatomyositis and malignancy has been known since 1976, when a review of 258 cases between 1916 to the mid-1970s reported a 5-fold to 7-fold increase in the incidence of malignancies in patients with dermatomyositis.[24] The risk of underlying malignancy seems to be less impressive with polymyositis and inclusion body myositis. As an example, a study by Buchbinder and colleagues[25] found 116 malignancies in a total of 537 subjects with biopsy-proven inflammatory myopathy. The highest risk for malignant disease was associated with dermatomyositis (SIR 6.2). Cancer risk was also increased in polymyositis but only with a SIR of 2.0 and similarly so for inclusion-body myositis (SIR 2.4). The likelihood of associated cancer diminished with passage of time (SIR 4.4 in the first year, 3.4 between 1 and 3 years, 2.2 between 3 and 5 years, and 1.6 beyond 5 years [P for trend = .002]).[25] Patients with cancer-associated dermatomyositis have been reported to have more severe cutaneous lesions, dysphagia, and diaphragmatic involvement, and to be older.[26]

Vasculitides

The paraneoplastic vasculitides comprise approximately 2% to 5% of all vasculitic syndromes. LCV accounts for 50% to 60% of paraneoplastic vasculitides and is the

most common paraneoplastic vasculitis in both hematologic malignancies and solid tumors.[27] The diagnosis is generally confirmed by skin biopsy, which shows neutrophilic inflammation of vessel walls with endothelial swelling and fibrinoid necrosis in postcapillary venules. Paraneoplastic Henoch-Schönlein purpura (HSP) is a form of LCV and accounts for 15% of paraneoplastic vasculitides. HSP has been reported in association with carcinomas of the lung and urogenital and gastrointestinal tracts. The 2 key patient characteristics of the paraneoplastic forms of HSP are male sex (95%) and older age. In addition, renal involvement is more common in this form of HSP.[28]

Polyarteritis nodosa is a form of vasculitis that accounts for 15% of all paraneoplastic vasculitides and predominantly involves small and medium-sized vessels of the skin, peripheral nervous, and gastrointestinal systems. Hairy cell leukemia is rare and only accounts for 2% of all leukemias. It is arguably the malignancy with the strongest association with paraneoplastic polyarteritis nodosa. One of the possible mechanisms for this association is presumed to be the cross-reactivity of antibodies against hairy cell leukemic cells with vascular endothelial cells.[29]

Paraneoplastic Musculoskeletal Syndromes

Paraneoplastic syndromes are characterized by symptoms that are mediated through hormones and cytokines produced by tumors. Through a variety of cellular or humoral mechanisms, these conditions result in clinical manifestations at sites away from the primary tumor or its metastases. Paraneoplastic musculoskeletal syndromes can involve the joints, fasciae, muscles, vessels, or bones. The symptoms generally occur within 2 years of onset of the clinical signs of malignancy, and may be clues for early detection of an occult malignancy. There is a growing list of musculoskeletal syndromes associated with malignancy, which ranges from paraneoplastic synovitis to erythromelalgia. However, a causal relationship between the rheumatologic manifestations and underlying malignancy needs to be established for the symptoms to be considered paraneoplastic. For example, prompt regression of the symptoms after successful treatment of the underlying cancer confirms the association.

Indeed, few syndromes have been found to satisfy the Bradford Hill criteria for causation.[4] The musculoskeletal syndromes with strongest data supporting their paraneoplastic nature include HOA, cancer-associated myositis, paraneoplastic polyarthritis, RS3PE syndrome, palmar fasciitis and polyarthritis (PFPAS), and tumor-induced osteomalacia.

Hypertrophic osteoarthropathy

HOA was first recognized in 1889 by von Bamberger.[30] The clinical association of HOA with underlying lung malignancy was established a few decades later.[31] Patients may present with tibial and femoral bone pain and arthralgia. The physical examination can show soft tissue tenderness in the symptomatic regions, synovitis of the adjacent joints, and clubbing of the digits. Conventional radiographs may show periosteal osseous proliferation. Technetium bone scan further documents increased uptake in the periosteum and involved joints. Acanthosis palmaris (or tripe palms) is a less-recognized finding in patients with HOA and cancer, which presents as hyperkeratosis of the palms with prominence of the dermatoglyphic palmar lines and a gyrated, velvety appearance to the palmar skin.[32] The underlying etiologic factor is thought to be overproduction of several growth factors. One such growth factor is platelet-derived growth factor, which can be released from the small vessels of the fingertips in response to platelet aggregates that have bypassed the lung capillary network in various cardiac and pulmonary diseases. This may cause increased vascularity,

permeability, and mesenchymal cell growth that promote new bone formation and clubbing.[33]

Vascular endothelial growth factor (VEGF) is also an important cytokine in the pathogenesis of HOA. Although hypoxemia itself is a strong stimulus for VEGF production, the highest levels of VEGF have been noted in patients with underlying malignancy. VEGF induces vascular hyperplasia, new bone formation, and edema. Removal of the lung tumors results in decreased circulating VEGF levels and at least one reported case of resolution of the skeletal abnormalities.[34] Periostitis and bone pain usually respond well to prostaglandin inhibition by nonsteroidal antiinflammatory drugs. The refractory cases have been treated with zoledronate in some instances.[35]

Paraneoplastic polyarthritis

Described as an acute onset, RA-like, polyarthritis associated with malignancy, paraneoplastic polyarthritis was first described by Pines and colleagues[36] in 1984. There have since been numerous articles describing this clinical syndrome. The demographics of this condition are different from that of RA, owing to a higher incidence in men (male/female ratio of 1.7:1) and an older median age of onset (approximately 54.2 years). Hematologic or lymphoproliferative malignancies comprise about one-third of the cases. The most frequent solid tumors are adenocarcinomas of the lung and breast, although colon cancer and other solid tumors have also been reported. The arthritis is usually of sudden onset. Patients have significantly elevated C-reactive protein and erythrocyte sedimentation rate. Seropositivity does not rule out the paraneoplastic nature of the arthritis. A total of 27.2% tested positive for rheumatoid factor and 19.0% tested positive for antinuclear antibodies.[32] Anticitrullinated protein antibodies can also be present in patients with paraneoplastic arthritis. One case series reported anticitrullinated protein antibody positivity in 7 of 65 subjects (10.7%).[37] One of the distinguishing characteristics of this form of arthritis is its lack of response to corticosteroids and other disease-modifying antirheumatic drugs. Typically, the arthritis resolves with adequate treatment of the underlying malignancy. A case series of 26 subjects with paraneoplastic arthritis noted that, in cases in which the tumor relapsed, 75% of the patients did not experience a relapse of their rheumatic symptoms.[38]

Palmar fasciitis and polyarthritis syndrome

This rare paraneoplastic disorder was first described as shoulder-hand syndrome in 1966 by Bermer.[39] It was not until 1982 when Medsger and colleagues[40] described it as a separate entity in 6 postmenopausal women with malignant ovarian tumors in whom PFPAS developed. These symptoms preceded the diagnosis of adenocarcinoma of the ovary by 5 to 25 months. All had bilateral pain and limitation of range of motion of the shoulders and hands, and prominent PFPAS of several other joints. All subjects had nonresectable tumors with ascites and peritoneal metastatic seeding. Histologic characteristics included endometrioid carcinoma, poor tumor differentiation, and unusually severe stromal proliferation of fibrous tissue. These subjects did not respond to corticosteroids or chemotherapy, and all subjects died 2 to 17 months after diagnosis of the neoplasm.[40] A comprehensive review in 2014 described the characteristic features of PFPAS in 100 cases. Most subjects had a sudden onset of diffuse painful swelling of both the hands along with marked stiffness. The subjects subsequently had nodular thickening of the palmar fascia that was similar to Dupuytren contracture but much more severe, with loss of function owing to flexion contractures. Similar symptoms were observed in the feet of 20% of subjects, reflecting plantar fascia involvement. Some cases had erythematous or acrocyanotic

discoloration, but only one satisfied the classic Raynaud description. Sclerodactyly was absent and capillary microscopy was normal. Some investigators describe advanced cases as possessing so-called woody hands. Occasionally, the term groove sign was used, describing an indentation of the skin over superficial veins when the extremity was raised. The pattern of joint involvement included synovitis of metacarpophalangeal, proximal interphalangeal, and wrists. Adhesive capsulitis of the shoulders was common. Ovarian adenocarcinoma was the most frequent tumor reported (36.8%). Ovarian, breast, and other malignancies of the female reproductive tract comprise 50% of the published cases. Interestingly, inflammatory markers are not particularly elevated, with near-normal erythrocyte sedimentation rate noted in 50% and mild elevation only of C-reactive protein in 70% of cases.[41] Fibroblast proliferation and increased production of extracellular matrix components are key histologic features of PFPAS. However, the role of soluble stimulators of fibroblast activity, such as transforming growth factor β or connective tissue growth factor, is yet to be proven. A markedly elevated serum soluble interleukin-2 receptor level was noted in one case of gastric carcinoma, suggesting a component of lymphocyte activation in the disease pathogenesis.[42]

Remitting seronegative symmetric synovitis with pitting edema

RS3PE is characterized by symmetric synovitis of small joints in extremities coupled with significant pitting edema. Patients are usually of advanced age and have negative serology for RA. The condition is briskly responsive to treatment with low-dose corticosteroids. However, a review of the 5 small case series of RS3PE (89 total subjects) found malignancy in 22 subjects (24.7%) shortly after the onset of symptoms. Five of these cases were of hematopoietic origin. No significant demographic or clinical differences were observed between idiopathic and paraneoplastic cases of RS3PE.[32] VEGF plays a significant role in RS3PE pathogenesis and may explain the synovial hypervascularity and vascular permeability (edema) seen in this condition. Elevated levels of matrix metalloproteinase 3 have been noted in the sera of subjects with paraneoplastic form of RS3PE.[43] Both idiopathic and paraneoplastic RS3PE often respond to low-dose prednisone, although the response in the paraneoplastic form can be less dramatic or delayed.[43]

Multicentric reticulohistiocytosis

MRH is a rare multisystem granulomatous non–Langerhans cell histiocytosis that presents with severe arthritis and can result in rapid joint destruction. This potentially mutilating arthritis also involves the skin, with dermal infiltration of CD68-positive histiocytes and multinucleated giant cells possessing an eosinophilic ground-glass cytoplasm. These cells form coral-red papular skin lesions (with Köbner phenomenon) and can also involve the tendon sheath, synovium, and bone; and, less commonly, liver, salivary glands, kidneys, lymph nodes, heart, and lungs.[44] Several other conditions have been reported in association with MRH, including a positive skin tuberculin test (12%–50%), systemic vasculitis, and a variety of underlying internal malignancies (15%–30% of the cases). The malignancies usually occur within 3 years of MRH manifestations and include bronchial, breast, stomach, cervical, and liver carcinomas.[45] MRH is relatively resistant to glucocorticoids, methotrexate, and hydroxychloroquine. However, it may respond to tumor necrosis factor α inhibition and to parenteral administration of alendronate.[46]

Erythromelalgia

Erythromelalgia is an uncommon disorder that is defined by the presence of an intense burning pain, increased temperature, and redness of the skin, without evidence of

arterial circulatory compromise. The lower extremities are usually involved, and symptoms are worsened by heat and dependency, and improve with cooling and elevation of the affected part. The adult form may be idiopathic but 18% of cases occur in patients with polycythemia vera and essential thrombocythemia. Symptoms of erythromelalgia may precede the development of thrombocytosis by a median of 2.5 years. Interestingly, the disease manifestations in patients with myeloproliferative disorders can sometimes be effectively reversed by a single daily dose of acetylsalicylic acid. The other myeloproliferative disorders associated with erythromelalgia include polycythemia vera, essential thrombocythemia, agnogenic myeloid metaplasia, myelofibrosis, and chronic myelogenous leukemia.[47] In addition, erythromelalgia has been associated with solid organ malignancies such as breast, prostate, ovary, and colon carcinomas, as well as thymoma.[48]

Sweet syndrome (acute febrile neutrophilic dermatosis)

Sweet syndrome presents with fever, neutrophilia, arthralgia, and erythematous, tender skin lesions comprising nonvasculitic dermal neutrophilic infiltration. The skin lesions are usually on the face, neck, dorsum of the hands, and upper extremities. The lesions are tender and nonpruritic and may have vesicular and pustular components. The most common underlying malignancies associated with Sweet syndrome are myelogenous leukemia and myelodysplastic syndromes, although association with solid tumors, lymphomas, and plasma cell dyscrasias have also been reported.[49]

Canale-Smith stiff-person or stiff-man syndrome

Canale-Smith stiff-person syndrome (SPS) is a rare condition that presents with progressive muscular rigidity and spasm involving the axial muscles. SPS has been reported in association with several other autoimmune conditions, including type I diabetes and thyroiditis, vitiligo, and pernicious anemia. Approximately 35% of SPS patients have type I diabetes.[50]

Glutamic acid decarboxylase (GAD) is an enzyme selectively concentrated in neurons secreting the neurotransmitter γ-aminobutyric acid and in pancreatic β cells. Autoantibodies against GAD have been reported in patients with SPS and concurrent epilepsy and insulin-dependent diabetes mellitus. The presence of this antibody in 20 of 33 patients with SPS has been reported in a previous case series and may be helpful for the diagnosis of this condition.[51] Diabetics have antibodies against a different epitope than the one seen in SPS patients, and their symptoms may start distally and occur in only one limb.

A paraneoplastic SPS has been reported in patients with breast cancer and small cell lung cancers. These patients do not have anti-GAD and antiislet cell antibodies but may have antibodies against amphiphysin, which is a cytoplasmic protein. Amphiphysin Ab-associated SPS usually occurs in older women with breast cancer and has predilection for involvement of the cervical region. The symptoms respond to benzodiazepines and, at times, corticosteroids treatment. Patients usually experience dramatic improvement after successful treatment of the underlying cancer.[52] Another antibody in patients with SPS is directed against the α1 subunit of the glycine receptor. Patients with this antibody usually do not have cancer but can have progressive encephalomyelitis and myoclonus.[53]

Tumor-induced osteomalacia or oncogenic osteomalacia

This rare paraneoplastic syndrome presents with bone pain, weakness, multiple fractures, height loss, and gait abnormalities. Tumor-induced osteomalacia has been described in association with small mesenchymal tumors that secrete the phosphaturic hormone and fibroblast growth factor 23, with related abnormalities in phosphate

and vitamin D metabolism. Laboratory investigations typically show hypophosphatemia caused by renal phosphate wasting, inappropriately normal or low 1,25-dihydroxy vitamin D, and elevated or inappropriately normal plasma fibroblast growth factor 23. In addition, a tumor-induced osteomalacia-like syndrome can also be seen in association with other diseases, such as prostate cancer, oat cell cancer, hematologic malignancies, neurofibromatosis, epidermal nevus syndrome, and polyostotic fibrous dysplasia of bone.[54]

Polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes syndrome (poems syndrome)

This rare paraneoplastic syndrome is usually secondary to a plasma cell dyscrasia. Patients may also present with papilledema, extravascular volume overload, sclerotic bone lesions, thrombocytosis, and Castleman disease (angiofollicular lymph node hyperplasia). The diagnosis can be confirmed in the presence of elevated blood levels of VEGF.[55]

Eosinophilic fasciitis

Eosinophilic fasciitis is characterized by symmetric limb or trunk erythema and edema, followed by the orange peel (peau d'orange) appearance of the skin and subsequent collagenous thickening of the subcutaneous fascia. Eosinophilia is present early in the course of the disease, and the disease spares the skin of the hands and feet. Elevation of an affected limb causes visible indentation along the course of the superficial veins (ie, groove sign). Associated hematologic conditions may include aplastic anemia, myelodysplastic and myeloproliferative disorders, lymphoma, multiple myeloma, and lymphocytic and eosinophilic leukemia.[56]

Lupus-like syndromes

Subacute cutaneous lupus erythematosus (SCLE) is a photosensitive, nonscarring rash that can be seen in association with SLE in 50% of cases; it can also be idiopathic or drug-induced. Eighty percent of patients with SCLE have positive results for anti-Ro/SSA antibodies. There are a few reports of SCLE arising in the setting of malignancies such as small cell lung cancer.[57] In addition, patients with multiple myeloma and other paraproteinemias can present with positive antinuclear antibodies.

Polymyalgia rheumatica–like syndrome

PMR is a disease of older adults who may present with shoulder and hip girdle muscle pain and stiffness. The definitive diagnosis is challenging because of the extensive list of conditions presenting with similar symptoms. A trial of low-dose corticosteroids is commonly met with a prompt and dramatic improvement in the symptoms. A PMR-like paraneoplastic syndrome has been described in association with myelodysplastic diseases and rarely in metastatic cancers. Corticosteroid therapy in these cases does not result in dramatic response. However, successful treatment of the underlying malignancy results in regression of symptoms. When a diagnosis of PMR is established, clues to a potentially fruitful investigation for underlying malignancy include an earlier age of onset, an asymmetric presentation, a sedimentation rate less than 40 or more than 100 mm per hour, a poor response to low dose glucocorticoids, and prominent constitutional symptoms.[58]

Pyogenic arthritis

Septic arthritis caused by unusual organisms, such as clostridium septicum[59] and streptococcus bovis,[60] should prompt the search for an occult colon cancer.

SUMMARY

A variety of neoplastic syndromes can present with mucocutaneous and musculoskeletal manifestations and mimic rheumatic conditions. On the other hand, certain autoimmune conditions and associated therapies can result in a higher incidence of particular types of malignancies. Awareness of these associations will result in appropriate screening and more vigilant monitoring of patients at risk.

There is also an expanding array of paraneoplastic conditions that may present as the sole manifestation of an occult malignancy. Therefore, timely recognition of these entities prompt looking for an underlying, otherwise difficult-to-diagnose, malignancy. This would likely result in early diagnosis and appropriate treatment of the associated cancer and better long-term outcome.

It is also critical to suspect an underlying neoplastic condition because certain rheumatologic conditions are unusually refractory to the conventional therapy.

REFERENCES

1. Kankeleit H. Uber primare nichteirige Polymyositis. Dtsch Arch Klin Med 1916; 120:335–49.
2. Zintzaras E, Voulgarelis M, Moutsopoulos HM. The risk of lymphoma development in autoimmune diseases: a meta-analysis. Arch Intern Med 2005;165(20): 2337–44.
3. Naschitz JE. Rheumatic syndromes: clues to occult neoplasia. Curr Opin Rheumatol 2001;13(1):62–6.
4. Hill AB. The environment and disease: association or causation? Proc R Soc Med 1965;58(5):293–300.
5. Villa AR, Kraus A, Alarcon-Segovia D. Autoimmune rheumatic diseases and cancer: evidence of causality?. In: Shoenfeld Y, Gershwin ME, editors. Cancer and autoimmunity. Amsterdam (the Netherlands): Elsevier; 2000. p. 111–7.
6. Naschitz JE, Rosner I, Rozenbaum M, et al. Rheumatic syndromes: clues to occult neoplasia. Semin Arthritis Rheum 1999;29(1):43–55.
7. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin 2016; 66(1):7–30.
8. WHO classification of tumours of soft tissue and bone. In: Fletcher CMD, Bridge JA, Hogendoorn PCW, et al, editors. World Health Organization classification of tumours. 4th edition. Lyon (France): International Agency for Research on Cancer; 2013.
9. Garnero P, Buchs N, Zekri J, et al. Markers of bone turnover for the management of patients with bone metastases from prostate cancer. Br J Cancer 2000;82: 858–64.
10. Isomäki H, Hakulinen T, Joutsenlahti U. Excess risk of lymphomas, leukemia and myeloma in patients with rheumatoid arthritis. J Chronic Dis 1978;31:691–6.
11. Chakravarty EF, Genovese MC. Associations between rheumatoid arthritis and malignancy. Rheum Dis Clin North Am 2004;30(2):271–84.
12. Huang WK, Chiou MJ, Kuo CF, et al. No overall increased risk of cancer in patients with rheumatoid arthritis: a nationwide dynamic cohort study in Taiwan. Rheumatol Int 2014;34(10):1379–86.
13. Baron JA. Epidemiology of non-steroidal anti-inflammatory drugs and cancer. Prog Exp Tumor Res 2003;37:1–24.
14. Shah A, Diehl LF, St Clair EW. T cell large granular lymphocyte leukemia associated with rheumatoid arthritis and neutropenia. Clin Immunol 2009;132(2): 145–52.

15. Prochorec-Sobieszek M, Rymkiewicz G, Makuch-Łasica H, et al. Characteristics of T-cell large granular lymphocyte proliferations associated with neutropenia and inflammatory arthropathy. Arthritis Res Ther 2008;10(3):R55.
16. Gayed M, Bernatsky S, Ramsey-Goldman R, et al. Lupus and cancer. Lupus 2009;18(6):479–85.
17. Bernatsky S, Boivin JF, Joseph L, et al. An international cohort study of cancer in systemic lupus erythematosus. Arthritis Rheum 2005;52(5):1481–90.
18. Bernatsky S, Ramsey-Goldman R, Labrecque J, et al. Cancer risk in systemic lupus: an updated international multi-center cohort study. J Autoimmun 2013; 42:130–5.
19. Löfström B, Backlin C, Sundström C, et al. A closer look at non-Hodgkin's lymphoma cases in a national Swedish systemic lupus erythematosus cohort: a nested case-control study. Ann Rheum Dis 2007;66(12):1627–32.
20. Kim SC, Glynn RJ, Giovannucci E, et al. Risk of high-grade cervical dysplasia and cervical cancer in women with systemic inflammatory diseases: a population-based cohort study. Ann Rheum Dis 2015;74:1360–7.
21. Pontifex EK, Hill CL, Roberts-Thomson P. Risk factors for lung cancer in patients with scleroderma: a nested case-control study. Ann Rheum Dis 2007;66:551–3.
22. Shah AA, Rosen A, Hummers L, et al. Close temporal relationship between onset of cancer and scleroderma in patients with RNA polymerase I/III antibodies. Arthritis Rheum 2010;62:2787.
23. Derk CT, Rasheed M, Artlett CM, et al. A cohort study of cancer incidence in systemic sclerosis. J Rheumatol 2006;33:1113–6.
24. Barnes BE, Mawr B. Dermatomyositis and malignancy. A review of the literature. Ann Intern Med 1976;84(1):68–76.
25. Buchbinder R, Forbes A, Hall S, et al. Incidence of malignant disease in biopsy-proven inflammatory myopathy. A population-based cohort study. Ann Intern Med 2001;134(12):1087–95.
26. Ponyi A, Constantin T, Garami M, et al. Cancer-associated myositis: clinical features and prognostic signs. Ann N Y Acad Sci 2005;1051:64–71.
27. Fain O, Hamidou M, Cacoub P, et al. Vasculitides associated with malignancies: analysis of sixty patients. Arthritis Rheum 2007;57(8):1473–80.
28. Park HJ, Ranganathan P. Neoplastic and paraneoplastic vasculitis, vasculopathy, and hypercoagulability. Rheum Dis Clin North Am 2011;37(4):593–606.
29. Hasler P, Kistler P, Gerber H. Vasculitides in hairy cell leukemia. Semin Arthritis Rheum 1995;25(2):134–42.
30. von Bamberger E. Veränderungen der Röhrenknochen bei Bronchiektasie. Wien Klin Wochenschr 1889;2:226–40 [in German].
31. Craig JW. Hypertrophic pulmonary osteoarthropathy as the first symptom of pulmonary neoplasm. Br Med J 1937;1:750–2.
32. Manger B, Schett G. Paraneoplastic syndromes in rheumatology. Nat Rev Rheumatol 2014;10(11):662–70.
33. Dickinson CJ, Martin JF. Megakaryocytes and platelet clumps as the cause of finger clubbing. Lancet 1987;2:1434–5.
34. Olán F, Portela M, Navarro C, et al. Circulating vascular endothelial growth factor concentrations in a case of pulmonary hypertrophic osteoarthropathy. J Rheumatol 2004;31:614–6.
35. Jayakar BA, Abelson AG, Yao Q. Treatment of hypertrophic osteoarthropathy with zoledronic acid: case report and review of the literature. Semin Arthritis Rheum 2011;41:291–6.

36. Pines A, Kaplinsky N, Olchovsky D, et al. Rheumatoid arthritis-like syndrome: a presenting symptom of malignancy. Report of 3 cases and review of the literature. Eur J Rheumatol Inflamm 1984;7(2):51–5.
37. Kisacik B, Onat AM, Kasifoglu T, et al. Diagnostic dilemma of paraneoplastic arthritis: case series. Int J Rheum Dis 2014;17(6):640–5.
38. Morel J, Deschamps V, Toussirot E, et al. Characteristics and survival of 26 patients with paraneoplastic arthritis. Ann Rheum Dis 2008;67:244–7.
39. Bermer C. Shoulder hand syndrome. A case of unusual etiology. Ann Phys Med 1967;9:168–71.
40. Medsger TA, Dixon JA, Garwood VF. Palmar fasciitis and polyarthritis associated with ovarian carcinoma. Ann Intern Med 1982;96:424–31.
41. Manger B, Schett G. Palmar fasciitis and polyarthritis syndrome—systematic literature review of 100 cases. Semin Arthritis Rheum 2014;44(1):105–11.
42. Enomoto M, Takemura H, Suzuki M, et al. Palmar fasciitis and polyarthritis associated with gastric carcinoma: complete resolution after gastrectomy. Intern Med 2000;39:754–7.
43. Origuchi T, Arima K, Kawashiri SY, et al. High serum matrix metalloproteinase 3 is characteristic of patients with paraneoplastic remitting seronegative symmetrical synovitis with pitting edema syndrome. Mod Rheumatol 2012;22:584–8.
44. Tajirian AL, Malik MK, Robinson-Bostom L, et al. Multicentric reticulohistiocytosis. Clin Dermatol 2006;24:486–92.
45. Hu L, Mei JH, Xia J, et al. Erythema, papules, and arthralgia associated with liver cancer: report of a rare case of multicentric reticulohistiocytosis. Int J Clin Exp Pathol 2015;8(3):3304–7.
46. Goto H, Inaba M, Kobayashi K, et al. Successful treatment of multicentric reticulohistiocytosis with alendronate: evidence for a direct effect of bisphosphonate on histiocytes. Arthritis Rheum 2003;48(12):3538.
47. Kurzrock R, Cohen PR. Paraneoplastic erythromelalgia. Clin Dermatol 1993; 11(1):73–82.
48. Han JH, Lee JB, Kim SJ, et al. Paraneoplastic erythromelalgia associated with breast carcinoma. Int J Dermatol 2012;51(7):878–80.
49. Cohen PR, Kurzrock R. Sweet's syndrome revisited: a review of disease concepts. Int J Dermatol 2003;42:761–78.
50. Rakocevic G, Floeter MK. Autoimmune stiff person syndrome and related myelopathies: understanding of electrophysiological and immunological processes. Muscle Nerve 2012;45(5):623–34.
51. Solimena M, Folli F, Aparisi R, et al. Autoantibodies to GABA-ergic neurons and pancreatic beta cells in stiff-man syndrome. N Engl J Med 1990;322(22): 1555–60.
52. Murinson BB, Guarnaccia JB. Stiff-person syndrome with amphiphysin antibodies: distinctive features of a rare disease. Neurology 2008;71(24):1955–8.
53. Hutchinson M, Waters P, McHugh J, et al. Progressive encephalomyelitis, rigidity, and myoclonus: a novel glycine receptor antibody. Neurology 2008;71(16): 1291–2.
54. Chong WH, Molinolo AA, Chen CC, et al. Tumor-induced osteomalacia. Endocr Relat Cancer 2011;18(3):R53–77.
55. Dispenzieri A. POEMS syndrome. Blood Rev 2007;21(6):285–99.
56. Lakhanpal S, Ginsburg WW, Michet CJ, et al. Eosinophilic fasciitis: clinical spectrum and therapeutic response in 52 cases. Semin Arthritis Rheum 1988;17(4): 221–31.

57. Evans KG, Heymann WR. Paraneoplastic subacute cutaneous lupus erythematosus: an under-recognized entity. Cutis 2013;91(1):25–9.
58. Naschitz JE, Slobodin G, Yeshurun D, et al. Atypical polymyalgia rheumatica as a presentation of metastatic cancer. Arch Intern Med 1997;157:2381.
59. Dylewski J, Luterman L. Septic arthritis and *Clostridium septicum*: a clue to colon cancer. CMAJ 2010;182(13):1446–7.
60. Garcia-Porrua C, Gonzalez-Gay MA, Monterroso JR, et al. Septic arthritis due to Streptococcus bovis as presenting sign of 'silent' colon carcinoma. Rheumatology 2000;39(3):338–9.

Update on Sjögren Syndrome and Other Causes of Sicca in Older Adults

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KEYWORDS

• Sjögren syndrome • Dry eye • Aging • Salivary hypofunction • Xerostomia

KEY POINTS

- Dryness of the eyes, mouth, and other mucosal membranes (sicca) is reported by up to 30% of persons over the age of 65.
- Sjögren syndrome is the prototypical autoimmune illness that causes dry eyes and dry mouth and is an important consideration in individuals presenting with these symptoms.
- Diagnosis requires the presence of anti-SSA and/or anti-SSB antibodies, or a minor salivary gland biopsy showing at least 1 tightly aggregated periductal lymphocytic aggregate per 4 mm^2 of glandular tissue section.
- Management requires attention to both the glandular (ocular and oral dryness, glandular enlargement) and extraglandular manifestations (eg, arthritis, pneumonitis, nephritis, vasculitis).

INTRODUCTION

Henrik Sjögren used the term "sicca syndrome" to describe the disease that he studied extensively during his lifetime, beginning with a comprehensive analysis of 19 patients that he completed in 1933 as an ophthalmologist in training.[1,2] The characteristic phenotypic features included severe ocular and oral mucosal dryness

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afflicting most often postmenopausal women, many of whom had associated rheumatoid arthritis. Sicca syndrome and Sjögren syndrome became synonymous. However, we now know that most older adults with sicca syndrome (ie, oral and ocular mucosal dryness) do not have Sjögren syndrome. As currently defined, Sjögren syndrome is a systemic rheumatic disease with autoimmune-induced inflammation of the lacrimal and salivary glands, resulting in impaired tear and saliva production. The distinction between these 2 entities is important, because the identification of those patients with an autoimmune basis for their sicca manifestations is the first step in deciding whether therapies directed at the immune system might be beneficial and avoiding such therapies and their attendant risks in patients with nonautoimmune sicca syndrome.

This article reviews the clinical manifestations, differential diagnosis, and medical evaluation of older adults with dry eyes and mouth, as well as the approach to the diagnosis and management of Sjögren syndrome.

EPIDEMIOLOGY OF SICCA

Symptoms of dryness of the eyes, mouth, and vagina (in women) increase with age and reach up to 30% in persons more than the age of 65 years, particularly in women.[3–9] Objective evidence of diminished tear or saliva production is much less frequent,[6,7,10] indicating the weak association between dryness symptoms and objective measures. Both dry eye and dry mouth symptoms were reported by 4.4% of an elderly population, age 65 to 84 years, in Salisbury, Maryland,[11] and had no association with markers of systemic autoimmunity. The prevalence of Sjögren syndrome in this population was only 0.04%.[12]

DRY EYE

Dry eye manifests most often with ocular irritation, including burning, stinging, soreness, and a foreign body sensation. The symptoms are aggravated by exposure to low humidity, wind, or air drafts, as well as prolonged visual attention, including reading. Less frequent symptoms include blurred vision, excess tearing, and blepharospasm.

Dry eye is generally caused by diminished tear production or by excessive tear evaporation[13] (**Box 1**). The former is most often caused by lacrimal gland disease,

Box 1
Common causes of dry eye

Aqueous Tear Deficiency	Evaporative Tear Deficiency
• SS • Age-related dry eye • Systemic medications (eg, antihistamines, β-blockers, antispasmodics, diuretics) • Lacrimal gland duct obstruction (eg, cicatricial pemphigoid, mucous membrane pemphigoid, trachoma, erythema multiforme, burns) • Ocular sensory loss leading to reflex hyposecretion (eg, diabetes mellitus, corneal surgery, contact lens wear, trigeminal nerve injury) • Lacrimal gland infiltration (eg, sarcoid, lymphoma, graft vs host disease, AIDS, IgG4-related disease)	• Meibomian gland dysfunction (posterior blepharitis) • Exophthalmos, poor lid apposition, lid deformity • Low blink rate • Ocular surface disorders (eg, vitamin A deficiency, toxicity from topical drugs/preservatives, contact lens wear) • Ocular surface disease (eg, allergic conjunctivitis)

Abbreviations: Ig, immunoglobulin; SS, Sjögren syndrome.

but can result from lacrimal gland duct obstruction or reflex hyposecretion related to corneal sensory loss. Excessive evaporation from Meibomian gland dysfunction and other forms of blepharitis is more common. Other causes of dryness include incomplete lid closure during sleep, allergic conjunctivitis, and trachoma.

The assessment of dry eye requires multiple tests (**Box 2**). The Schirmer test measures tear production[14] and can be performed reliably by a rheumatologist in a clinic setting. A sterile rectangular strip of filter paper, rounded and notched at the proximal end, is folded over the lower eyelid at the midpoint between the middle and lateral fornix of each eye. The patient is then asked to close the eyes gently during the 5-minute duration of the test. The extent of tear wicking or wetting is recorded in millimeters. The Schirmer test can be performed with or without anesthesia to measure basal and reflex tear secretion, respectively. Without anesthesia, a Schirmer test result of less than 5 mm in at least 1 eye is abnormal. This test is imperfect in the elderly, because the degree of wetting decreases with age. In 2 population-based surveys of elderly individuals (≥65 years), the prevalence of an abnormal Schirmer test ranged from 12% to 58%.[4,6]

Ocular surface staining with vital dyes allows slit lamp visualization of devitalized conjunctival cells and corneal epithelial defects. It is more sensitive than the Schirmer test for detecting dry eye. Lissamine green is most commonly used to stain the conjunctiva and fluorescein the cornea. The extent of ocular surface staining is a measure of dryness-induced ocular surface damage, is one of the classification criteria for Sjögren syndrome, and can be scored using methods described by van Bijsterveld[15] and by the Sjögren International Collaborative Clinical Alliance.[16,17]

The tear breakup time test is used to assess the stability of the tear film[18] and is typically abnormal in Meibomian gland dysfunction. Tear osmolarity measurement[19,20] is the best for predicting dry eye severity.[20]

XEROSTOMIA AND SALIVARY HYPOFUNCTION

Symptoms of dry mouth, termed xerostomia, include burning, dry lips, alteration of taste, and a sense of having an inadequate amount of saliva. There also may be difficulty speaking, swallowing, and wearing dentures. The need to sip water to swallow dry food is an important marker of reduced salivary function.[21] Halitosis, painful tongue fissures, mucosal ulcers, and pain with ingestion of spicy or acidic foods

Box 2
Tests used to assess dry eye disease

Test	Abnormal Value	Significance of Abnormal Test
Schirmer	<5 mm/5 min in either eye	Inadequate tear production
Ocular surface staining	Score ≥4 (von Bijsterveld)[15] Score ≥3 (SICCA)[17]	Damage to the ocular surface
Tear breakup time	<10 s	Poor tear film stability, as seen in Meibomian gland dysfunction
Tear osmolarity	≥308 mOsm/L in either eye	Excessive tear evaporation, lacrimal gland disease, or ocular surface inflammation

Abbreviation: SICCA, Sjögren's International Collaborative Clinical Alliance.

Data from van Bijsterveld OP. Diagnostic tests in the sicca syndrome. Arch Ophthalmol 1969;82(1):10–4; and Whitcher JP, Shiboski CH, Shiboski SC, et al. A simplified quantitative method for assessing keratoconjunctivitis sicca from the Sjögren's syndrome International Registry. Am J Ophthalmol 2010;149(3):405–15.

may stem from candidal overgrowth on the oral mucosa. The relation between salivation and xerostomia is complex. Dawes[22] showed that healthy patients report dry mouth symptoms when their baseline salivary flow is reduced by 50%, even if the residual salivary flow level remains within the broad range of normal.

Saliva is produced by the major (parotid, submandibular, sublingual) and myriad submucosal minor salivary glands. The parotid glands only produce saliva on gustatory or olfactory stimulation. Saliva is continually secreted by the sublingual, submandibular, and minor salivary glands. This basal secretion is crucial for maintaining oral health.

Both unstimulated and stimulated salivary flow rates are measured. Saliva that pools in the mouth without stimulation can be collected for 5 to 15 minutes, providing a measure of so-called whole saliva production in a clinic setting (**Box 3**). It is considered the most relevant measure of oral health. Stimulated whole salivary flow rates can be measured with the patient chewing gum, preweighed gauze, or paraffin (eg, Parafilm) and are not generally affected by medication use. With special research techniques, stimulated (eg, with lemon juice on the tongue) and unstimulated saliva flow rates can be measured from the individual parotid glands or sublingual/submandibular glands.

Human salivary glands undergo atrophy with age (**Fig. 1**). In morphometric studies, aging was associated with acinar loss and replacement with fat and connective tissue.[23,24] Whole unstimulated saliva flow rates decrease with age, which may contribute to the age-dependent increase in dental caries.[25] However, this is not true for stimulated parotid saliva flow rates.[26]

There are multiple potential causes for xerostomia and salivary hypofunction (**Box 4**).[10] Side effects from medications commonly used in older individuals are the most common.

VAGINAL DRYNESS

Vaginal dryness, dyspareunia, and vulvar pruritus are common symptoms among postmenopausal women. These symptoms relate to menopause-related decreases in the levels of estrogen and other sex steroids, but can also have other causes.

Box 3
Measurement of unstimulated whole salivary flow rate

Unstimulated whole saliva collection measures saliva production under resting or basal conditions. The patient should not have had anything to eat or drink for 90 minutes before the procedure. The use of a parasympathomimetic should be discontinued for 12 hours before the procedure, and the use of artificial saliva should be stopped 3 hours before. During the collection procedure, the patient is instructed to minimize actions that can stimulate saliva (talking, increased orofacial movement) and should not swallow. At time 0, any saliva present in the mouth is cleared by swallowing. For the subsequent 5 minutes, any saliva collected in the mouth is emptied into a preweighed tube every minute (ie, 5 times). This collecting tube then is weighed to determine a postcollection weight. The difference between the precollection and postcollection weight is determined, and this represents the unstimulated whole saliva production for 5 minutes. To convert to a volume of saliva from the weight of saliva, an assumption is made that saliva is similar to water, with 1 g of water/saliva at 4°C equaling 1 mL of saliva/water.

Less than 0.100 mL/min is considered a reduced unstimulated salivary flow rate.

From Wu AJ. Optimizing dry mouth treatment for individuals with Sjögren's syndrome. Rheum Dis Clin North Am 2008;34(4):1004; with permission.

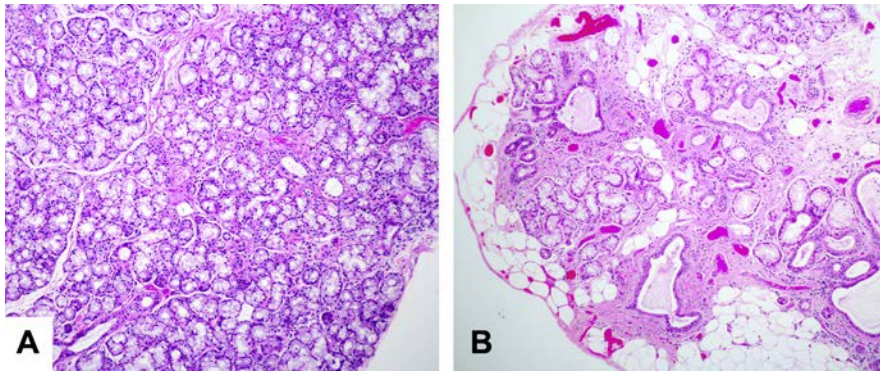

Fig. 1. Histopathology of minor labial salivary glands. The sections are from biopsies of a 28-year-old woman (*A*) and a 65-year-old woman (*B*), shown at the same magnification. Neither had Sjögren syndrome. (*A*) This histopathologic section shows normal tissue, with confluent mucous acini and normal-sized intralobular ducts. (*B*) In contrast, this section shows extensive acinar loss, interstitial fibrosis, ductal dilatation, and fatty replacement. These changes are often seen to varying degrees in older patients (stain: hematoxylin and eosin; original magnification ×100).

In 2014, 2 international societies recommended that the range of symptoms and signs associated with menopause be termed the genitourinary syndrome of menopause.[27] These symptoms include genital dryness, burning, irritation, inadequate lubrication, dyspareunia, urinary urgency, dysuria, and recurrent urinary tract infections. Similar symptoms are also seen with infectious vaginitis, irritant or allergic vulvitis or vaginitis, vulvovaginal dermatoses, hypertonic pelvic floor muscle dysfunction, painful bladder syndrome/interstitial cystitis, vulvodynia, and pudendal neuralgia.[27]

In women affected by Sjögren syndrome, vaginal dryness can be severe and affect sexual ability and pleasure.[28] There is scant information regarding the cause of this dryness. One hypothesis is that the Skene and related glands of the vaginal introitus are affected in the same manner as exocrine glands found elsewhere.[29] There has been no histopathologic confirmation of this theory to date. Biopsies of vaginal mucosa from patients with Sjögren syndrome show subepithelial inflammatory infiltrates more frequently than those from controls.[30] A negative effect of this infiltrate on the transudation of serous fluid into the vaginal vault constitutes an alternative hypothesis for vaginal dryness in women with Sjögren syndrome.

Box 4
Common causes of dry mouth

- Medications, including antidepressants, anticholinergics, antispasmodics, antihypertensives, antihistamines, sedatives, and diuretics
- Sjögren syndrome
- Diabetes mellitus
- Head and neck irradiation
- Dehydration
- Parkinson disease

SJÖGREN SYNDROME

Sjögren syndrome is the prototypical illness of dryness of the eyes and mouth. It is a chronic systemic autoimmune disease characterized by dry eyes and dry mouth, arising from autoimmune-induced inflammation of the lacrimal and salivary glands. This chronic inflammatory process gradually leads to glandular injury and related dysfunction over the course of years, eventually causing the cardinal symptoms of dry eyes and mouth. It primarily affects perimenopausal and postmenopausal women and can occur in a primary form or in association with another systemic autoimmune disease (termed secondary Sjögren syndrome). The reported prevalence of primary Sjögren syndrome in population-based studies ranges from 0.01% to 0.09%.[31] Sjögren syndrome is present in up to 17% of patients with rheumatoid arthritis.[32,33] Because the latter is a disease whose prevalence reaches 1.1% in the United States,[34] this renders Sjögren syndrome the second most common systemic rheumatic disease. Key features are shown in **Box 5**.

Sjögren syndrome disease onset is uncommon after the age of 65 or 70 years.[35,36] Older patients with Sjögren syndrome, compared with younger ones, have a lower frequency of serologic abnormalities, such as anti-SSA, anti-SSB, rheumatoid factor, and hyperglobulinemia.[37] Parotid enlargement, arthralgia, and Raynaud phenomenon are also less common, although higher frequencies of lung involvement and anemia have been noted.[36] A distinct subset of older patients with Sjögren syndrome with anticentromere antibodies is characterized by the Raynaud phenomenon, overlap features of limited systemic sclerosis, and more severe salivary and lacrimal gland dysfunction.[38]

The clinical presentation of Sjögren syndrome is varied, but is most often that of mucosal dryness (**Box 6**).

Sjögren syndrome is associated with a variety of systemic manifestations (**Box 7**). Some are direct manifestations of the disease, whereas others represent coincidental autoimmune diseases. Apart from symptoms of fatigue, joint pain, and mild cognitive impairment (often termed brain fog), the prevalence of these organ-specific manifestations is each less than 20%.[39]

Box 5
Key clinical features of Sjögren syndrome

- Predominant involvement of women, with female to male ratios of more than 10:1.
- Diagnosis most commonly established in the fifth and sixth decades of life, although symptoms of dryness may precede the diagnosis by many years.
- Affects individuals across the age spectrum, including children, but most commonly women in the perimenopausal years of life.
- Extraglandular manifestations in approximately 50% of patients, including constitutional symptoms (eg, fatigue and mild cognitive impairment) and other systemic manifestations, with involvement of diverse organ systems.
- Presence of anti-SSA/Ro and anti-SSB/La in 60% to 80% of patients.[71–74]
- Increased risk of B-cell non-Hodgkin lymphoma, particularly MALT and diffuse B-cell lymphoma. The relative risk of non-Hodgkin lymphoma ranges from 4.8 for primary to 9.6 for secondary SS,[75] with an estimated lifetime risk of 5% to 10%.[76]

Abbreviation: MALT, mucosa-associated lymphoid tissue.
Data from Refs.[71–76]

Box 6
Modes of presentation of Sjögren syndrome

- Symptoms or signs of dry eyes and mouth
- Episodic or persistent salivary gland enlargement
- Sudden increase in dental caries
- An established connective tissue disease complicated by dry eyes or mouth
- Extraglandular disease (eg, annular erythema, cryoglobulinemia, peripheral neuropathy, or interstitial pneumonitis)
- Abnormal serologic test, such as anti-SSA and/or anti-SSB antibodies
- MALT lymphoma of a salivary gland

Abbreviation: MALT, mucosa-associated lymphoid tissue.

The natural history is generally one of stability, with a slow decline in lacrimal and salivary gland function. Patients may report periods of worsening sicca or fatigue and uncommonly have the types of systemic disease flares seen in systemic lupus or rheumatoid arthritis. There is no increase in overall mortality according to a recent metaanalysis, but patients with specific extraglandular manifestations, including those with vasculitis, cryoglobulinemia, pulmonary disease, and lymphoma, have been identified as having higher mortality.[40,41]

Box 7
Systemic manifestations of Sjögren syndrome

Organ Involvement	Manifestation
Constitutional	Fatigue
	Mild cognitive disturbance
Musculoskeletal	Arthritis/arthralgia
	Myositis (especially inclusion body myositis)
Cutaneous	Annular erythema
	Xerosis
	Palpable purpura
Pulmonary	Interstitial pneumonitis
	Follicular bronchiolitis
Vascular	Raynaud's phenomenon
	Vasculitis
Gastrointestinal	Atrophic gastritis
	Primary biliary cirrhosis
Endocrine	Autoimmune thyroid disease
Cardiac	Pericarditis
Renal	Interstitial nephritis with renal tubular acidosis
	Membranoproliferative glomerulonephritis
Hematologic	Leukopenia, neutropenia
	Thrombocytopenia
	Anemia
	Monoclonal gammopathy
	Cryoglobulinemia
Lymphoproliferative	Lymphoma
Neurologic	Peripheral neuropathy
	Ataxic ganglionopathy
	Myelitis (including neuromyelitis optica)

DIAGNOSIS OF SJÖGREN SYNDROME

The diagnosis requires evidence of autoimmune-induced inflammation targeting the salivary or lacrimal glands. In 2016, a new set of classification criteria was jointly endorsed by the American College of Rheumatology and the European League against Rheumatism (**Box 8**).[42] These criteria have supplanted 2 previous sets, those of the American-European Consensus Group (2002) and the American College of Rheumatology (2012).[43,44] The new criteria incorporate elements of these previous sets and eliminate some that were outdated, but maintain the requirement that the

Box 8
ACR-EULAR classification criteria for primary SS

Item	Weight/Score
The classification of primary SS applies to any individual who meets the inclusion criteria,[a] does not have any of the conditions listed as exclusion criteria,[b] and has a score of ≥4 when the weights from the 5 criteria items below are summed:	
Labial salivary gland with focal lymphocytic sialadenitis and focus score of ≥1 foci/4 mm[b,c]	3
Anti-Ro/SSA positive	3
Ocular Staining Score of ≥5 (or van Bijsterveld score of ≥4) in ≥1 eye[d,e]	1
Schirmer's test of ≤5 mm/5 min in ≥1 eye[d]	1
Unstimulated whole saliva flow rate of ≤0.1 mL/min[d,f]	1

Abbreviations: ACR-EULAR, American College of Rheumatology-European League against Rheumatism; SS, Sjögren syndrome.

[a] Inclusion criteria: these criteria are applicable to any patient with at least 1 symptom of ocular or oral dryness, defined as a positive response to at least 1 of the following questions: (1) Have you had daily, persistent, troublesome dry eyes for more than 3 months? (2) Do you have a recurrent sensation of sand or gravel in the eyes? (3) Do you use tear substitutes more than 3 times a day? (4) Have you had a daily feeling of dry mouth for more than 3 months? (5) Do you frequently drink liquids to aid in swallowing dry food?; or in whom there is suspicion of SS from the European League Against Rheumatism SS Disease Activity Index questionnaire (at least 1 domain with a positive item).

[b] Prior diagnosis of any of the following conditions would exclude diagnosis of SS and participation in SS studies or therapeutic trials because of overlapping clinical features or interference with criteria tests: History of head and neck radiation treatment; active hepatitis C infection (with positive polymerase chain reaction); AIDS; sarcoidosis; amyloidosis; graft-versus-host disease; immunoglobulin G4-related disease.

[c] Labial salivary gland with focal lymphocytic sialadenitis and a focus score of ≥1 foci/4 mm^2. The histopathologic examination should be performed by a pathologist with expertise in the diagnosis of focal lymphocytic sialadenitis, and a focus score count following a protocol described in Daniels TE, Cox D, Shiboski CH, et al. Associations between salivary gland histopathologic diagnoses and phenotypic features of Sjögren's syndrome among 1,726 registry participants. Arthritis Rheum 2011;63:2021–30.

[d] Patients who are normally taking anticholinergic drugs should be evaluated for objective signs of salivary hypofunction and ocular dryness after a sufficient interval off these medications for these components to be a valid measure of oral and ocular dryness.

[e] Ocular staining score described by Whitcher JP, Shiboski CH, Shiboski SC, et al. A simplified quantitative method for assessing keratoconjunctivitis sicca from the Sjögren's Syndrome International Registry. Am J Ophthalmol 2010;149(3):405–15. VB: van Bijsterveld score described in Van Bijsterveld OP. Diagnostic tests in the Sicca syndrome. Arch Ophthalmol 1969;82:10–4.

[f] UWS: unstimulated whole saliva described in Navazesh M, Kumar SK, University of Southern California School of Dentistry. Measuring salivary flow: challenges and opportunities. J Am Dent Assoc 2008;139 Suppl:35S–40S.

From Shiboski CH, Shiboski SC, Seror R, et al. 2015 Classification criteria for Sjögren's syndrome: a consensus and data-driven methodology involving three international patient cohorts. Arthritis Rheum 2017;69:35–45.

diagnosis of Sjögren syndrome be only tenable if a patient has either anti-SSA antibodies or a "positive" minor salivary gland biopsy (focal lymphocytic sialadenitis with a focus score greater than or equal to 1).

These criteria are only applicable to an individual with findings concerning for Sjögren syndrome, defined as at least 1 symptom of ocular or oral dryness (positive response to $\geq$1 of 5 standardized questions), salivary gland enlargement, or a characteristic extraglandular manifestation of Sjögren syndrome (as defined by a positive domain in the European League against Rheumatism Sjögren Syndrome Disease Activity Index).[45]

The authors use these current classification criteria as a general guide, and establish the diagnosis if a patient has an objective measure of ocular and/or oral dryness or characteristic imaging abnormalities (eg, by ultrasound imaging, MRI, or computed tomography scanning), coupled with anti-SSA antibodies or a positive lip biopsy.

The authors recommend that patients suspected of having Sjögren syndrome be evaluated as follows.

- History, seeking a history of persistent symptoms of dry eyes and/or mouth. Validated screening questions are included in the American College of Rheumatology-European League against Rheumatism Classification Criteria (see **Box 8**, footnote).
- Examination, seeking signs of salivary hypofunction and of a systemic rheumatic disease
  1. Oral examination
     a. Is there enlargement of the lacrimal or major salivary glands? What is the texture of the major salivary glands? Are there discrete nodules or masses?
     b. Does saliva pool under the elevated tongue when observed over the course of 1 minute?
     c. Does the tongue have deep fissures, a hyperlobulated appearance, or absence of filiform papillae on its surface?
     d. The Challacombe scale, available online, can be used to identify and rate the severity of oral dryness, based on physical examination findings (http://www.challacombescale.co.uk/Challacombe-Scale-ENG.pdf, accessed February 11, 2018).[46]
  2. General examination
     a. Look for sclerodactyly, palpable purpura, synovitis, basilar pulmonary rales.
- Laboratory testing
  1. Screen for antinuclear antibody (tested by immunofluorescence assay), anti-SSA (Ro), and anti-SSB (La), and rheumatoid factor. Anti-SSA and anti-SSB antibodies can be present despite a negative antinuclear antibody test.
  2. A complete blood count, urinalysis, and chemistry profile may reveal abnormalities supportive of Sjögren syndrome, including leukopenia and neutropenia, hyperglobulinemia, renal impairment, and proteinuria.
- Ophthalmologic examination
  1. Schirmer testing is an appropriate initial test. A formal ophthalmologic examination serves not only to confirm the diagnosis of dry eye but also to define the contributing causes, such as Meibomian gland dysfunction and conjunctivochalasis. Guidelines for this evaluation can be found at https://sicca-online.ucsf.edu/documents/eye-exam-SOP.pdf.
- Sialometry
  1. Documentation of salivary hypofunction is only necessary if the eye examination does not show dry eye disease (see **Box 3**).

- Labial gland biopsy
  1. A labial gland biopsy, best performed by an oral surgeon, is required for diagnosis if the patient lacks anti-SSA and/or anti-SSB antibodies. The biopsy also has value in excluding alternative diagnoses (eg, sarcoid, amyloid, mucosa-associated lymphoid tissue lymphoma, and immunoglobulin [Ig] G4–related disease). Guidelines for its performance can be found at https://sicca-online.ucsf.edu/documents/Oral-Saliva-SOP.pdf.
- Imaging (**Fig. 2**)
  1. Salivary gland ultrasound imaging is favored because of its low cost and lack of ionizing radiation. The presence of multiple ovoid hypoechoic lesions, often bounded by hyperechoic bands, correlates with markers of more severe disease. These imaging abnormalities have high specificity for the diagnosis, but only moderate sensitivity.[47–51]
  2. Computed tomography scanning is not recommended because of the radiation exposure. However, the presence of multiple punctate calcifications within the parotid glands has high specificity.[52]
  3. MRI of the parotid glands may reveal heterogeneity of signal intensity on both T1-weighted and T2-weighted images, with both hypointense and hyperintense foci measuring 1 to 4 mm in diameter.[53]

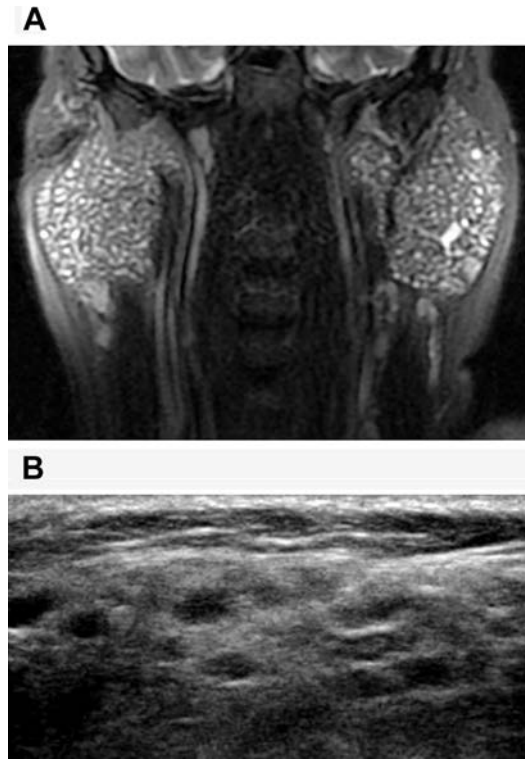

Fig. 2. Imaging techniques in Sjögren syndrome. This patient has bilateral symmetric parotid gland enlargement, seen best on the T2 fat-suppressed MRI (*A*). Note the multiple T2-hyperintense foci scattered throughout both glands, a characteristic finding. With ultrasound imaging (*B*), multiple hypoechoic rounded lesions with convex borders are noted throughout the glandular parenchyma. In normal parotid gland tissue, the parenchyma has a homogeneous appearance with ultrasound imaging.

Be aware of common pitfalls in the diagnostic evaluation. These include the following.

a. Assessment of sicca manifestations. Certain historical features distinguish the sicca manifestations of Sjögren syndrome from symptoms often experienced by otherwise healthy people. The symptoms of ocular and oral dryness should be a daily, persistent problem and have been present for at least 3 months. The ocular dryness should be severe enough to mandate the use of tear supplements at least 3 times per day. Positive responses to the following 2 questions are highly predictive of salivary hypofunction[21]: Do you sip liquids to aid in swallowing dry foods? Does your mouth feel dry when eating a meal? The ophthalmologist's assessment of a dry eye patient for Sjögren syndrome should include a Schirmer test and conjunctival staining with Lissamine green (as opposed to simply assessing corneal staining with fluorescein), because positive results of these 2 tests correlate best with positive serology and positive lip biopsy.[54]
b. Antibody testing. Antibodies to SSA and SSB are not specific. They are found in systemic lupus and inflammatory myopathies, and are seen in up to 0.9% of healthy women in the US population.[55] With modern multiplex assay technology, weakly positive test results for anti-SSA and anti-SSB must also be interpreted with caution, because they have a less robust association with Sjögren syndrome. In particular, the finding of anti-SSB antibodies alone, in the absence of anti-SSA antibodies, does not support a diagnosis of Sjögren syndrome[56] and has, thus, been eliminated as a classification criterion for the disease.[42] The authors recommend the performance of a labial gland biopsy in the diagnostic evaluation of patients with weakly positive anti-SSA or anti-SSB antibodies (or anti-SSB alone), in whom Sjögren syndrome is suspected.
   A commercial assay for 3 murine tissue-specific autoantibodies, carbonic anhydrase 6, parotid-specific protein, and salivary protein-1, is now available as a test for early Sjögren syndrome. However, the ability of these antibodies to mark individuals who are destined to develop Sjögren syndrome has not been validated.[57]
c. Labial gland biopsy performance and interpretation. The histopathology of the minor salivary gland, termed focal lymphocytic sialadenitis, is characterized by lymphocytic aggregates that surround intralobular salivary ducts (**Fig. 3**) and

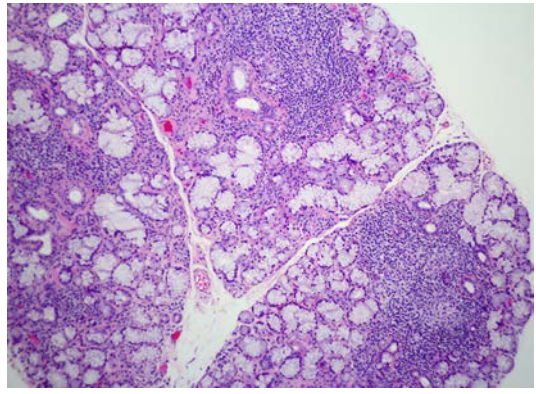

Fig. 3. Focal lymphocytic sialadenitis. This section of a labial salivary gland biopsy shows the typical features of focal lymphocytic sialadenitis. Note the tightly aggregated lymphocytes surrounding ducts and adjacent to normal-appearing mucous acini. At least 3 foci are evident (stain: hematoxylin and eosin; original magnification ×100).

are adjacent to normal-appearing mucus-secreting acini. The number of these lymphocytic aggregates per 4 mm^2 of glandular tissue section equates to the focus score. A score greater than or equal to 1 is a criterion for the classification of Sjögren syndrome and has been validated as the best cutoff value differentiating Sjögren syndrome from non-Sjögren syndrome controls.[58] Accurate assessment of the focus score requires adequate glandular tissue for analysis; ideally, 3-5 glands should be collected at the time of biopsy and the total surface area of the glandular surface area should be at least 4 mm^2 (preferably 10–20 mm^2 because the focus score can be overestimated in smaller specimens).[58] The total glandular surface area of the tissue section should be measured with a calibrated reticule in the microscope eyepiece or with digital image software. Because chronic inflammation of the salivary gland can also arise from ductal obstruction and other forms of glandular injury, care must be taken to exclude from the focus score lymphocytic aggregates in areas of severe acinar loss, ductal dilatation, and fibrosis (**Fig. 4**). Assessment of the labial gland biopsy for Sjögren syndrome may require that the slides be forwarded to a reference laboratory for interpretation and proper calculation of the focus score.

The differential diagnosis of Sjögren syndrome primarily includes alternative causes of sicca symptoms, salivary and/or lacrimal gland enlargement, and the characteristic serologic abnormalities.

- Sicca complex in the elderly: age-related interstitial fibrosis, acinar atrophy, and nonspecific chronic inflammation in the labial gland biopsy may be misinterpreted as indicating Sjögren syndrome (see **Fig. 4**).
- Salivary and/or lacrimal gland enlargement: Particular attention should be paid to the possibility of lymphoma. IgG-4 related disease is most common in older men. It may present as unilateral submandibular gland enlargement (Küttner tumor) or parotid and lacrimal gland enlargement. Other diagnostic possibilities include amyloid infiltration, sarcoidosis, human immunodeficiency virus infection, bulimia, and hyperlipoproteinemia.[59]

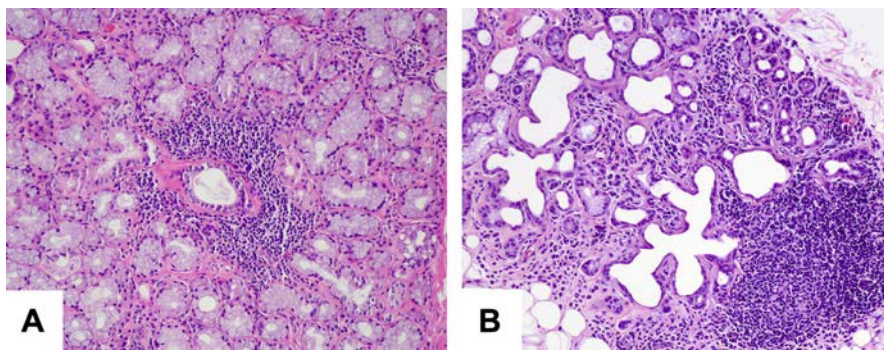

Fig. 4. Potential misinterpretation of labial gland biopsies. (*A*) The lymphocytic focus is typical of that seen in focal lymphocytic sialadenitis, being centered on a duct and adjacent to normal-appearing mucus-secreting acini. (*B*) In contrast, the lymphocytic focus here is present within a gland lobule marked by interstitial fibrosis, ductal dilatation, and marked acinar loss. This focus should not be interpreted as representative of Sjögren syndrome (stain: hematoxylin and eosin; original magnification ×100).

- Serologic abnormalities: antinuclear antibodies, rheumatoid factor, and monoclonal proteins are more prevalent in the elderly population.[55] Thus, positive tests must be interpreted cautiously when they coincide with symptoms or signs of oral or ocular dryness.

MANAGEMENT OF SJÖGREN SYNDROME

Most patients only require topical and systemic treatments directed at alleviating their ocular, oral, and vaginal dryness; preventing dental decay; and managing oral candidiasis. Patients with systemic manifestations, including those with joint pain, skin lesions, and internal organ involvement, may benefit from immunomodulatory treatments. All patients with Sjögren syndrome require monitoring for disease complications, especially lymphoma. The British Society for Rheumatology has recently established guidelines for the management of Sjögren syndrome.[60]

The management of ocular dryness depends on its severity and the patient's response to therapy.[61] Avoidance of wind and smoke, and the use of protective eyewear, can be helpful for all patients. Artificial tears with a demulcent (eg, methylcellulose, propylene glycol, and glycerin) are a mainstay of treatment. Patients should use preservative-free drops if drops are instilled 4 or more times a day. Use of thicker ocular gels and ointments before bed can help with the dryness that occurs during sleep. Supplementation of the diet with omega-3 essential fatty acids has been shown to be of benefit. The use of topical cyclosporine and steroid solutions can be useful in a variety of dry eye conditions, but should be undertaken in consultation with an ophthalmologist. Punctal plugs to preserve tears are often used in moderate to severe dry eye. Patients with more severe dry eye disease may require the use of moisture chamber spectacles, autologous serum tears, contact lenses, or scleral prostheses.

The prevention of oral dryness includes maintaining good hydration and avoiding medications that worsen dryness. Patients should be counseled to be more aware of factors that can aggravate dryness, such as low-humidity environments and mouth breathing. Frequent sips of oral solutions can be helpful, with options ranging from water to artificial saliva. Sucking on sugar-free hard candies helps to stimulate saliva flow. Oral hygiene and dental care are essential in preserving dentition in persons with pathologic oral dryness.

Muscarinic agonists, such as pilocarpine and cevimeline, can substantially increase saliva and, to a lesser extent, tear flow. However, overall tolerance of these agents may be hampered by cholinergic side effects of excessive sweating, increased urinary frequency, flushing, chills, rhinitis, nausea, and diarrhea. Care must be taken when these medications are prescribed to the elderly.

Vaginal moisturizers and lubricants, including olive and vitamin E oils, are initial treatment options for vaginal dryness. Vitamin E capsules can be opened and the oil used in and around the vagina. A suppository containing hyaluronic acid, vitamin E, and vitamin A, used once daily for 14 days, then once every other day for the next 2 weeks, can be effective.[62] Obtaining these suppositories requires a compounding pharmacist. Low-dose vaginal estrogen therapy is indicated if symptoms do not improve with these nonprescription measures. The available options include a vaginal cream, insert, ring, or soft gel capsule.[63]

Hydroxychloroquine is commonly used for the management of joint pain and/or fatigue. However, clinical trials with this drug have shown mixed results, with none showing major clinical improvements.[64–66] The effect of immunosuppressive therapies on the glandular manifestations has been disappointing to date. The effect of

rituximab on Sjögren syndrome dryness is still being evaluated, with potential benefit being observed in a small, double-blind, placebo-controlled trial,[67] but not in 2 larger ones.[68,69] Prolonged therapy may be required for benefit.[70]

SUMMARY

Dryness of the eyes and mouth is a prevalent symptom in the population, especially among the elderly, and is most often related to the side effects of medications. However, there is a broad differential diagnosis for each symptom, and careful evaluation is important to define the cause and correct treatment. Sjögren syndrome is the prototypic disease that leads to these symptoms and primarily affects perimenopausal women. The diagnosis requires demonstration of an autoimmune disease underlying the sicca manifestations, either serologically or pathologically. Management can involve both topical and systemic therapies.

REFERENCES

1. Sjögren H. On knowledge of the keratoconjunctivitis sicca. VII. The sicca syndrome–an autoimmune disease. Acta Ophthalmol (Copenh) 1968;46(2):201–6.
2. Sjögren H. Zur Kenntnis der Keratoconjunctivitis sicca (Keratitis filiformis bei Hypofunktion der Tränendrüsen). Acta Ophthalmol (Copenh) 1933;11(Suppl 2):1–151.
3. Johansson AK, Johansson A, Unell L, et al. Self-reported dry mouth in Swedish population samples aged 50, 65 and 75 years. Gerodontology 2012;29(2):e107–15.
4. Lin PY, Tsai SY, Cheng CY, et al. Prevalence of dry eye among an elderly Chinese population in Taiwan: the Shihpai Eye Study. Ophthalmology 2003;110(6):1096–101.
5. Billings RJ, Proskin HM, Moss ME. Xerostomia and associated factors in a community-dwelling adult population. Community Dent Oral Epidemiol 1996;24(5):312–6.
6. Schein OD, Munoz B, Tielsch JM, et al. Prevalence of dry eye among the elderly. Am J Ophthalmol 1997;124(6):723–8.
7. Hay EM, Thomas E, Pal B, et al. Weak association between subjective symptoms or and objective testing for dry eyes and dry mouth: results from a population based study. Ann Rheum Dis 1998;57(1):20–4.
8. Orellana MF, Lagravere MO, Boychuk DG, et al. Prevalence of xerostomia in population-based samples: a systematic review. J Public Health Dent 2006;66(2):152–8.
9. Stapleton F, Alves M, Bunya VY, et al. TFOS DEWS II epidemiology report. Ocul Surf 2017;15(3):334–65.
10. Liu B, Dion MR, Jurasic MM, et al. Xerostomia and salivary hypofunction in vulnerable elders: prevalence and etiology. Oral Surg Oral Med Oral Pathol Oral Radiol 2012;114(1):52–60.
11. Schein OD, Hochberg MC, Munoz B, et al. Dry eye and dry mouth in the elderly: a population-based assessment. Arch Intern Med 1999;159(12):1359–63.
12. Hochberg MC, Schein OD, Munoz B, et al. The prevalence of dry eye, dry mouth, autoimmunity and primary Sjögren's syndrome in the general population. Arthritis Rheum 1996;39(Suppl):S66 [abstract].

13. The definition and classification of dry eye disease: report of the definition and classification subcommittee of the International Dry Eye WorkShop (2007). Ocul Surf 2007;5(2):75–92.
14. Cho P, Yap M. Schirmer test. I. A review. Optom Vis Sci 1993;70(2):152–6.
15. van Bijsterveld OP. Diagnostic tests in the Sicca syndrome. Arch Ophthalmol 1969;82(1):10–4.
16. Bron AJ, Evans VE, Smith JA. Grading of corneal and conjunctival staining in the context of other dry eye tests. Cornea 2003;22(7):640–50.
17. Whitcher JP, Shiboski CH, Shiboski SC, et al. A simplified quantitative method for assessing keratoconjunctivitis sicca from the Sjögren's Syndrome International Registry. Am J Ophthalmol 2010;149(3):405–15.
18. Sweeney DF, Millar TJ, Raju SR. Tear film stability: a review. Exp Eye Res 2013; 117:28–38.
19. Lemp MA, Bron AJ, Baudouin C, et al. Tear osmolarity in the diagnosis and management of dry eye disease. Am J Ophthalmol 2011;151(5):792–8.e1.
20. Potvin R, Makari S, Rapuano CJ. Tear film osmolarity and dry eye disease: a review of the literature. Clin Ophthalmol 2015;9:2039–47.
21. Fox PC, Busch KA, Baum BJ. Subjective reports of xerostomia and objective measures of salivary gland performance. J Am Dent Assoc 1987;115(4):581–4.
22. Dawes C. Physiological factors affecting salivary flow rate, oral sugar clearance, and the sensation of dry mouth in man. J Dent Res 1987;66 Spec No:648–53.
23. Scott J, Flower EA, Burns J. A quantitative study of histological changes in the human parotid gland occurring with adult age. J Oral Pathol 1987;16(10):505–10.
24. Syrjanen S. Age-related changes in structure of labial minor salivary glands. Age Ageing 1984;13(3):159–65.
25. Percival RS, Challacombe SJ, Marsh PD. Flow rates of resting whole and stimulated parotid saliva in relation to age and gender. J Dent Res 1994;73(8): 1416–20.
26. Ship JA, Pillemer SR, Baum BJ. Xerostomia and the geriatric patient. J Am Geriatr Soc 2002;50(3):535–43.
27. Portman DJ, Gass ML, Vulvovaginal Atrophy Terminology Consensus Conference Panel. Genitourinary syndrome of menopause: new terminology for vulvovaginal atrophy from the International Society for the Study of Women's Sexual Health and the North American Menopause Society. Menopause 2014;21(10):1063–8.
28. Maddali Bongi S, Del Rosso A, Orlandi M, et al. Gynaecological symptoms and sexual disability in women with primary Sjögren's syndrome and sicca syndrome. Clin Exp Rheumatol 2013;31(5):683–90.
29. Bloch KJ, Buchanan WW, Wohl MJ, et al. Sjögren's syndrome. a clinical, pathological, and serological study of sixty-two cases. Medicine (Baltimore) 1965;44: 187–231.
30. van Nimwegen JF, van der Tuuk K, Klinkert ER, et al. Subepithelial Infiltrate of the Vagina in Primary Sjögren's Syndrome: The Cause of Vaginal Dryness? [abstract]. Arthritis Rheumatol 2017;69(Suppl 10). Available at: http://acrabstracts.org/abstract/subepithelial-infiltrate-of-the-vagina-in-primary-sjogrens-syndrome-the-cause-of-vaginal-dryness/. Accessed May 3, 2018.
31. Qin B, Wang J, Yang Z, et al. Epidemiology of primary Sjögren's syndrome: a systematic review and meta-analysis. Ann Rheum Dis 2015;74(11):1983–9.
32. Uhlig T, Kvien TK, Jensen JL, et al. Sicca symptoms, saliva and tear production, and disease variables in 636 patients with rheumatoid arthritis. Ann Rheum Dis 1999;58(7):415–22.

33. Carmona L, Gonzalez-Alvaro I, Balsa A, et al. Rheumatoid arthritis in Spain: occurrence of extra-articular manifestations and estimates of disease severity. Ann Rheum Dis 2003;62(9):897–900.
34. Gabriel SE, Crowson CS, O'Fallon WM. The epidemiology of rheumatoid arthritis in Rochester, Minnesota, 1955-1985. Arthritis Rheum 1999;42(3):415–20.
35. Botsios C, Furlan A, Ostuni P, et al. Elderly onset of primary Sjögren's syndrome: clinical manifestations, serological features and oral/ocular diagnostic tests. Comparison with adult and young onset of the disease in a cohort of 336 Italian patients. Joint Bone Spine 2011;78(2):171–4.
36. Ramos-Casals M, Solans R, Rosas J, et al. Primary Sjögren syndrome in Spain: clinical and immunologic expression in 1010 patients. Medicine (Baltimore) 2008;87(4):210–9.
37. Haga HJ, Jonsson R. The influence of age on disease manifestations and serological characteristics in primary Sjögren's syndrome. Scand J Rheumatol 1999;28(4):227–32.
38. Baer AN, Medrano L, McAdams-DeMarco M, et al. Anti-centromere antibodies are associated with more severe exocrine glandular dysfunction in Sjögren's syndrome: analysis of the Sjögren's International Collaborative Clinical Alliance cohort. Arthritis Care Res (Hoboken) 2016;68(10):1554–9.
39. Brito-Zeron P, Ramos-Casals M, EULAR-SS Task Force Group. Advances in the understanding and treatment of systemic complications in Sjögren's syndrome. Curr Opin Rheumatol 2014;26(5):520–7.
40. Singh AG, Singh S, Matteson EL. Rate, risk factors and causes of mortality in patients with Sjögren's syndrome: a systematic review and meta-analysis of cohort studies. Rheumatology (Oxford) 2016;55(3):450–60.
41. Nannini C, Jebakumar AJ, Crowson CS, et al. Primary Sjögren's syndrome 1976-2005 and associated interstitial lung disease: a population-based study of incidence and mortality. BMJ Open 2013;3(11):e003569.
42. Shiboski CH, Shiboski SC, Seror R, 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 Rheumatol 2017;69(1):35–45.
43. Vitali C, Bombardieri S, Jonsson R, 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(6):554–8.
44. Shiboski SC, Shiboski CH, Criswell L, et al. American College of Rheumatology classification criteria for Sjögren's syndrome: a data-driven, expert consensus approach in the Sjögren's International Collaborative Clinical Alliance cohort. Arthritis Care Res (Hoboken) 2012;64(4):475–87.
45. Seror R, Bowman SJ, Brito-Zeron P, et al. EULAR Sjögren's syndrome disease activity index (ESSDAI): a user guide. RMD Open 2015;1(1):e000022.
46. Osailan SM, Pramanik R, Shirlaw P, et al. Clinical assessment of oral dryness: development of a scoring system related to salivary flow and mucosal wetness. Oral Surg Oral Med Oral Pathol Oral Radiol 2012;114(5):597–603.
47. Cornec D, Jousse-Joulin S, Pers JO, et al. Contribution of salivary gland ultrasonography to the diagnosis of Sjögren's syndrome: toward new diagnostic criteria? Arthritis Rheum 2013;65(1):216–25.
48. Takagi Y, Sumi M, Nakamura H, et al. Ultrasonography as an additional item in the American College of Rheumatology classification of Sjögren's syndrome. Rheumatology (Oxford) 2014;53(11):1977–83.

49. Theander E, Mandl T. Primary Sjögren's syndrome: diagnostic and prognostic value of salivary gland ultrasonography using a simplified scoring system. Arthritis Care Res (Hoboken) 2014;66(7):1102–7.
50. Baldini C, Luciano N, Tarantini G, et al. Salivary gland ultrasonography: a highly specific tool for the early diagnosis of primary Sjögren's syndrome. Arthritis Res Ther 2015;17:146.
51. Luciano N, Baldini C, Tarantini G, et al. Ultrasonography of major salivary glands: a highly specific tool for distinguishing primary Sjögren's syndrome from undifferentiated connective tissue diseases. Rheumatology (Oxford) 2015;54(12): 2198–204.
52. Sun Z, Zhang Z, Fu K, et al. Diagnostic accuracy of parotid CT for identifying Sjögren's syndrome. Eur J Radiol 2012;81(10):2702–9.
53. Takashima S, Takeuchi N, Morimoto S, et al. MR imaging of Sjögren syndrome: correlation with sialography and pathology. J Comput Assist Tomogr 1991; 15(3):393–400.
54. Bunya VY, Bhosai SJ, Heidenreich AM, et al. Association of dry eye tests with extraocular signs among 3514 participants in the Sjögren's syndrome international registry. Am J Ophthalmol 2016;172:87–93.
55. Satoh M, Chan EK, Ho LA, et al. Prevalence and sociodemographic correlates of antinuclear antibodies in the United States. Arthritis Rheum 2012;64(7):2319–27.
56. Baer AN, McAdams DeMarco M, Shiboski SC, et al. The SSB-positive/SSA-negative antibody profile is not associated with key phenotypic features of Sjögren's syndrome. Ann Rheum Dis 2015;74(8):1557–61.
57. Beckman KA, Luchs J, Milner MS, et al. The potential role for early biomarker testing as part of a modern, multidisciplinary approach to Sjögren's syndrome diagnosis. Adv Ther 2017;34(4):799–812.
58. Daniels TE, Cox D, Shiboski CH, et al. Associations between salivary gland histopathologic diagnoses and phenotypic features of Sjögren's syndrome among 1,726 registry participants. Arthritis Rheum 2011;63(7):2021–30.
59. Cornec D, Saraux A, Jousse-Joulin S, et al. The differential diagnosis of dry eyes, dry mouth, and parotidomegaly: a comprehensive review. Clin Rev Allergy Immunol 2015;49(3):278–87.
60. Price EJ, Rauz S, Tappuni AR, et al. The British Society for Rheumatology guideline for the management of adults with primary Sjögren's syndrome. Rheumatology (Oxford) 2017;56(10):1643–7.
61. Foulks GN, Forstot SL, Donshik PC, et al. Clinical guidelines for management of dry eye associated with Sjögren disease. Ocul Surf 2015;13(2):118–32.
62. Costantino D, Guaraldi C. Effectiveness and safety of vaginal suppositories for the treatment of the vaginal atrophy in postmenopausal women: an open, non-controlled clinical trial. Eur Rev Med Pharmacol Sci 2008;12(6):411–6.
63. Faubion SS, Sood R, Kapoor E. Genitourinary syndrome of menopause: management strategies for the clinician. Mayo Clin Proc 2017;92(12):1842–9.
64. Gottenberg JE, Ravaud P, Puechal X, et al. Effects of hydroxychloroquine on symptomatic improvement in primary Sjögren syndrome: the JOQUER randomized clinical trial. JAMA 2014;312(3):249–58.
65. Kruize AA, Hene RJ, Kallenberg CG, et al. Hydroxychloroquine treatment for primary Sjögren's syndrome: a two year double blind crossover trial. Ann Rheum Dis 1993;52(5):360–4.
66. Fox RI, Dixon R, Guarrasi V, et al. Treatment of primary Sjögren's syndrome with hydroxychloroquine: a retrospective, open-label study. Lupus 1996;5(Suppl 1): S31–6.

67. Meijer JM, Meiners PM, Vissink A, et al. Effectiveness of rituximab treatment in primary Sjögren's syndrome: a randomized, double-blind, placebo-controlled trial. Arthritis Rheum 2010;62(4):960–8.
68. Devauchelle-Pensec V, Mariette X, Jousse-Joulin S, et al. Treatment of primary Sjögren syndrome with rituximab: a randomized trial. Ann Intern Med 2014; 160(4):233–42.
69. Bowman SJ, Everett CC, O'Dwyer JL, et al. Randomized controlled trial of rituximab and cost-effectiveness analysis in treating fatigue and oral dryness in primary Sjögren's syndrome. Arthritis Rheumatol 2017;69(7):1440–50.
70. Carubbi F, Cipriani P, Marrelli A, et al. Efficacy and safety of rituximab treatment in early primary Sjögren's syndrome: a prospective, multi-center, follow-up study. Arthritis Res Ther 2013;15(5):R172.
71. Malladi AS, Sack KE, Shiboski SC, et al. Primary Sjögren's syndrome as a systemic disease: a study of participants enrolled in an international Sjögren's syndrome registry. Arthritis Care Res (Hoboken) 2012;64(6):911–8.
72. Theander E, Henriksson G, Ljungberg O, et al. Lymphoma and other malignancies in primary Sjögren's syndrome: a cohort study on cancer incidence and lymphoma predictors. Ann Rheum Dis 2006;65(6):796–803.
73. Lin DF, Yan SM, Zhao Y, et al. Clinical and prognostic characteristics of 573 cases of primary Sjögren's syndrome. Chin Med J (Engl) 2010;123(22):3252–7.
74. Ramos-Casals M, Brito-Zeron P, Perez-De-Lis M, et al. Sjögren syndrome or Sjögren disease? The histological and immunological bias caused by the 2002 criteria. Clin Rev Allergy Immunol 2010;38(2–3):178–85.
75. Ekstrom Smedby K, Vajdic CM, Falster M, et al. Autoimmune disorders and risk of non-Hodgkin lymphoma subtypes: a pooled analysis within the InterLymph Consortium. Blood 2008;111(8):4029–38.
76. Papageorgiou A, Ziogas DC, Mavragani CP, et al. Predicting the outcome of Sjögren's syndrome-associated non-Hodgkin's lymphoma patients. PLoS One 2015; 10(2):e0116189.

A Review of Osteoporosis in the Older Adult: An Update

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KEYWORDS

• Osteoporosis • Bisphosphonates • FRAX • Drug holiday • Hip fractures • Elderly • DXA

KEY POINTS

- Fractures and osteoporosis are common, especially in the elderly population. Hip fractures may be devastating.
- Osteoporosis in men is greatly unrecognized and untreated.
- Treatment of osteoporosis is generally recommended in postmenopausal women and men 50 years old or older who have a bone mineral density T-score of minus 2.5 or less, a history of previous spine or hip fracture, or a Who Fracture Risk Assessment Tool score indicating increased fracture risk.
- Bisphosphonates, teriparatide, and denosumab have proven to reduce risk of hip, vertebral, and nonvertebral fractures. Bisphosphonates are used usually as first-line treatment in patients if there are no contraindications. Teriparatide reduces the risk of nonvertebral and vertebral fractures.
- Individualizing therapy is important. This includes balancing the risks and benefits of bisphosphonates to enact a drug holiday. For patients at lower risk for fracture, drug holidays after 5 years of alendronate therapy or 3 years of zoledronic acid therapy can be considered.

INTRODUCTION

Osteoporosis is a disorder with major impact in Western society and globally, and osteoporotic fractures are associated with significant burden of health care cost, morbidity, and mortality.[1] Almost all patients remain undiagnosed and untreated, especially high-risk patients.[2] In patients 65 years and older, the increase in incidence of osteoporotic fractures is accompanied by grim effects on disability and mortality.[3]

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Older patients are at increased risk of nursing home admissions and long-term stay after hip osteoporotic fractures, as compared with myocardial infarctions and stroke.[4] In 2014, a discouraging study was published assessing the frequency of starting bisphosphonate treatment after hip fracture in the United States (2002–2011). In 2002, 40% of the patients started medication within 12 months of hip fracture, which decreased to less than 20% in 2011 nationwide.[5]

Osteoporosis is defined as a deterioration in bone mass and microarchitecture of bone, along with increased fragility, that predisposes bones to fracture.[6] Two main pathophysiologic processes generate bone loss. The first results from estrogen deficiency and affects trabecular bone, known as postmenopausal osteoporosis. This type of osteoporosis affects mainly women and is associated with vertebral fractures and hip fractures. Osteoblasts respond to many external and internal stimuli, including hormones (parathyroid hormone [PTH], vitamin D). As a result of these stimuli, macrophage colony-stimulating factor and membrane-bound receptor activator of nuclear factor-kappa B (RANK) ligand (RANKL) are produced. These, in turn, are critical factors for osteoclastogenesis. Binding of RANKL with its receptor RANK in osteoclasts stimulates their differentiation and prevents osteoclast cell death. Osteoprotegerin produced by osteoblasts inhibits the RANK-RANKL pathway.[7] Conversely, estrogen, transforming growth factor-β, and mechanical force inhibit RANKL expression, thus suppressing osteoclast cell formation and differentiation, ultimately decreasing bone resorption.[8]

Another advance in bone biology is the wingless-type mouse mammary tumor virus integration site (Wnt) signaling pathway in osteoblasts, which is important for bone formation. Inhibitors of this pathway are sclerostin and dickkopf Wnt signaling pathway inhibitor 1. Sclerostin is expressed in osteocytes as a response to mechanical stress.[9]

A second type, recently known as senile osteoporosis, mainly affects cortical bone, predisposing elderly patients to hip fractures. These changes in bone mass associated with aging are multifactorial; they include changes in hormones, as well as vitamin D insufficiency, leading to secondary hyperparathyroidism, thereby enhancing osteoclastic bone resorption. Recent evidence of a possible link between aging and senile osteoporosis has been described. Lack of lamin A/C, a special scaffolding protein found in bone structure cells, is seen in aging osteoblasts and is associated with reduced osteoblastic activity, lipodystrophy, and fat redistribution as observed in mice studies.[10]

Osteoporosis in men may be secondary to hypogonadism, corticosteroid use, and excessive alcohol use. In men, bone loss increases after age 70. Osteoporosis in men remains untreated and unrecognized.[11,12] In a study of elderly male nursing home residents with hip fractures, 66% of the patients had hypogonadism.[13] In elderly male patients, vertebral fractures are more common.[14] Testosterone depletion has direct effects on cortical and trabecular bone mass, resulting in decreased bone mineral density (BMD) in hypogonadal patients.[15] Osteoporosis is most often identified after the first hip fracture, which itself is a risk factor for future osteoporotic fractures.[12]

A comprehensive approach to the diagnosis and management of osteoporosis includes a detailed history, physical examination, BMD assessment, radiological studies to diagnose fractures, and a World Health Organization (WHO) Fracture Risk Assessment (FRAX) tool 10-year estimated fracture probability calculation. The diagnosis of osteoporosis by WHO criteria is established by BMD measurement using dual-energy x-ray absorptiometry (DXA) scanning or by adult vertebral or hip fracture in the absence of major trauma.[16] DXA measurement of the hip and spine is used to establish and confirm the diagnosis of osteoporosis. The BMD predicts fracture risk and has

been shown to correlate with bone strength and future fracture risk.[16] BMD is expressed in grams per square centimeters, and it is compared with an adult population of the same gender (T-score), or to the BMD of a reference population matched for age, sex, and ethnicity (Z-score). Osteoporosis and low bone mass have been defined based on DXA measurements (**Table 1**).

The National Osteoporosis Foundation (NOF) has established screening guidelines for osteoporosis. Routine screening with DXA should be performed in women aged 65 or older and postmenopausal women less than 65 year old based on risk factors. Screening should also be done in men older than 70 years old and men between 50 and 69 years old based on risk factors.[17]

To treat fractures and decrease mortality in this population of patients, vertebral imaging should be performed for surveillance of subclinical osteoporotic fractures in all women aged 70 years and older and all men 80 years and older if BMD T-score is less than or equal to −1.5 at the spine, total hip, or femoral neck. In postmenopausal women and men age 50 years and older with risk factors, such as historical height loss, low-trauma fracture, prospective height loss, or long-term corticosteroid treatment, performing vertebral imaging is also recommended.[16] Laboratory testing is recommended to exclude secondary causes such as multiple myeloma, gastrointestinal malabsorption, diabetes mellitus, primary hyperparathyroidism, inflammatory bowel disease, ankylosing spondylitis, and rheumatoid arthritis, among others. As part of the evaluation, a calcium and vitamin D level evaluation should be done.

The WHO FRAX score is used to estimate fracture risk in patients (https://www.shef.ac.uk/FRAX/tool). This tool applies to patients with low femoral neck BMD, between ages 40 and 90 years old. The FRAX score can be calculated with either femoral neck or total hip; however, when available, femoral neck is preferred.[18] The FRAX score is to be evaluated alongside clinical risk factors for fractures and can be used for both sexes (**Box 1**).

Osteoporosis treatment should be initiated in those patients with (1) hip or vertebral fractures, asymptomatic or clinical; (2) patients with T-scores less than or equal to −2.5 at the femoral neck, total hip, or lumbar spine by DXA; (3) in postmenopausal women and men aged 50 years and older with low bone mass (T-score between −1.0 and −2.5, osteopenia) at the femoral neck, total hip, or lumbar spine by DXA; and a 10-year hip fracture probability equal to or greater than 3% or a 10-year major osteoporosis-related fracture probability equal or greater than 20% based on the US-adapted WHO FRAX model (**Box 2**).[16,19]

There are several caveats when using this tool and clinical judgment must be used. In patients with low BMD in the lumbar spine but a normal femoral neck BMD, using

Table 1
Osteoporosis and low bone mass based on bone mineral density measurement by dual-energy x-ray absorptiometry

Category	Bone Mass Measurement
Normal	T-score greater than or equal to −1 SD
Osteopenia	T-score <−1 and >−2.5 SD
Osteoporosis	T-score less than or equal to −2.5 SD
Severe osteoporosis	T-score less than or equal to −2.5 in the presence of fracture

Abbreviation: SD, standard deviation.

Data from WHO scientific group on the assessment of osteoporosis at the primary health care level: summary meeting report, 2004. Geneva (Switzerland): World Health Organization; 2007.

Box 1
Clinical risk factors for fractures included in the Fracture Risk Assessment Tool

- History of smoking
- Alcohol abuse
- History of rheumatoid arthritis
- Secondary osteoporosis (inflammatory bowel disease, premature menopause, hypogonadism, chronic liver disease, malabsorption syndromes)
- Advanced age
- History of fractures
- History of glucocorticoid treatment
- Family history of hip fracture, parental
- Low body weight

Data from Kanis JA, Borgstrom F, De Laet C, et al. Assessment of fracture risk. Osteoporos Int 2005;16:581.

the FRAX tool tends to underestimate fracture risk. The FRAX tool also can underestimate the risk of fracture in patients with diabetes mellitus, which confers increased risk of fracture independent of FRAX-derived assessment with the BMD.[20] This tool has not been validated to be used in patients on current or previous osteoporosis treatment. Finally, patients who have been on a drug holiday for 1 to 2 years may be considered as untreated patients when using this tool.[21]

In terms of treatment options for osteoporosis, the NOF recommends starting with a nonpharmacologic approach. Resistance and weight-bearing exercise can increase muscle mass and transiently increase BMD.[22] Tai chi and yoga improve balance and increase muscle tone, which as a secondary effect reduces the risk for falls among elderly patients. Counseling about smoking cessation (which is directly linked to reduced BMD) and alcohol cessation are encouraged.[23] However, the efficacy of calcium and vitamin D treatment remains a controversial topic. Vitamin D supplementation has not been shown across-the-board to reduce the risk of fractures or to increase the BMD.[14] Meta-analyses of several large trials of calcium and vitamin D supplementation given separately suggested ineffectiveness preventing hip fracture. Given in combination, calcium and vitamin D was associated with an absolute risk reduction of 0.5% over 3 years, corresponding to a number needed to treat of 213

Box 2
Guidelines for treatment of osteoporosis

History of hip or vertebral fracture

T-score greater than or equal to −2.5 (DXA) at the femoral neck or spine

T-score between −1 and −2.5 at the femoral neck or spine, and a 10-year probability of hip fracture ≥3% or a 10-year probability of any major osteoporosis-related fracture ≥20% based on the US-adapted FRAX algorithm

Data from Cosman F, de Beur SJ, LeBoff MS, et al. Clinician's guide to prevention and treatment of osteoporosis. Osteoporos Int 2014;25:2359; and Watts NB, Adler RA, Bilezikian JP, et al. Osteoporosis in men: an endocrine society clinical practice guideline. J Clin Endocrinol Metab 2012;97:1802.

people treated for 3 years to prevent a hip fracture. For patients older than the age of 70 years, the absolute risk reduction was 0.9%.[24] In the Women's Health Initiative trial, women assigned to take calcium and vitamin D had an increase in BMD and a decrease by 12% in hip fracture compared with women assigned to placebo. There were no significant reductions in clinical vertebral fracture, fracture of the lower arm or wrist, or total fractures; however, they had a 17% higher risk of developing kidney stones compared with placebo. The mean calcium intake was approximately 1150 mg per day.[25] The NOF recommends that men aged 50 to 70 years consume 1000 mg per day of calcium and women aged 51 years and older and men aged 71 years and older consume 1200 mg per day of calcium. In terms of vitamin D supplementation, the NOF recommends an intake of 800 to 1000 IU of vitamin D per day for adults aged 50 years and older. At present, reasonable recommendations for postmenopausal women and men with osteoporosis is 1000 to 1500 mg per day of calcium and 600 to 800 IU per day of vitamin D.[16]

In a study by Amory and colleagues,[26] testosterone therapy with finasteride was used as treatment in older men with low serum testosterone levels (<200 ng/dL). After 3 years, an increase in BMD in the lumbar spine was observed. Finasteride also helped decrease the prostate growth and prostate-specific antigen levels. Testosterone therapy is also controversial. Its side effects may be detrimental because it can cause polycythemia, sleep apnea, and prostate cancer. Additional data are needed to safely use this agent in eugonadal men.

Pharmacologic therapies can be classified as antiresorptive, targeting osteoclast-mediated bone resorption; or anabolic, targeting stimulation of osteoblasts for new bone formation. Selective estrogen-receptor modulators (SERMs) activate tissue receptors for estrogen. Raloxifene is an SERM approved by the US Food and Drug Administration (FDA) to treat osteoporosis. It inhibits bone resorption, increases spine BMD, and decreases vertebral fractures but has no effect on nonvertebral or hip fractures.[27] Raloxifene decreases the risk of breast cancer among high-risk patients but increases thromboembolic events.[28]

Bisphosphonates inhibit bone remodeling, and both oral and intravenous (IV) forms have been shown in randomized trials to reduce risk of fractures. Side effects include gastric ulcers and reflux, and they should not be prescribed in patients with clinical significant esophageal disease, such as achalasia. In 2 Fracture Intervention Trials of Alendronate, paired randomized trials with 3 to 4 years follow-up involving postmenopausal women with a BMD T-score of −1.6 or less at the femoral neck, the rate of vertebral fractures was significantly lower by 50% among those who received alendronate compared with placebo.[29,30] Black and colleagues[29] studied women aged 55 to 81 years with low femoral neck BMD and at least one vertebral fracture at baseline, and enrolled them in 2 study groups based on presence or absence of an existing vertebral fracture. Women were randomly assigned to placebo or alendronate and followed up for 36 months. Among women with low bone mass and existing vertebral fractures, alendronate reduced the frequency of morphometric (radiological) and clinical vertebral fractures. In the second trial, Cummings and colleagues[30] evaluated women in the Fracture Intervention Trial without existing vertebral fractures. Women aged 54 to 81 years old with a femoral neck BMD of 0.68 g/cm^2 or less but no vertebral fracture were randomized to alendronate or placebo for 4 years. In women with low BMD but without vertebral fractures, 4 years of alendronate safely increased BMD and decreased the risk of first vertebral fracture. Alendronate significantly reduced the risk of clinical fractures among women with osteoporosis at femoral neck by 36% but not among women with higher BMD. Alendronate decreased the risk of radiographic vertebral fractures by 44% overall (number needed to treat, 60).

Two randomized controlled trials for risedronate are important: the Vertebral Efficacy with Risedronate Therapy (VERT) North America (NA) trial and the VERT-multinational (MN) trial. Harris and colleagues[31] (VERT-NA) studied postmenopausal women with existing vertebral fractures, low BMD in the spine, or both. Over a period of 3 years, the risk of fractures was lower by 49% with risedronate instead of placebo. A significant reduction was observed in the risk of new vertebral fractures by 65% and 61% after the first year of treatment with risedronate in VERT-NA and VERT-MN studies, respectively. This effect was maintained throughout the 3 years of treatment with significant reduction in the incidence of new vertebral fractures by 41% in VERT-NA and by 49% in VERT-MN. In VERT-NA, the risk of fractures in the first year of treatment in subjects with at least 2 or more vertebral fractures was 74%. Risedronate also significantly reduced the risk of nonvertebral fractures by 39% after 3 years in VERT-NA.[32] McClung and colleagues[33] studied the endpoint of hip fracture in the Hip Intervention Program. Risedronate (2.5 mg or 5 mg a day) was given to women 70 years or older who were at high risk for hip fracture; they showed a 30% reduction rate of hip fractures over 3 years as compared with placebo.

Chestnut and colleagues[34] studied ibandronate in a 3-year multicenter antifracture study. Subjects were randomized to treatment with either continuous oral ibandronate (2.5 mg daily), intermittent oral ibandronate (20 mg every other day for 12 doses every 3 months), or placebo. A 62% lower rate of vertebral fractures was observed compared with placebo; however, no reduction in rate of nonvertebral fractures was seen over a period of 3 years. Later, in the Monthly Oral Ibandronate in Ladies study, once-monthly ibandronate was compared with daily ibandronate. Substantial increases in lumbar spine BMD were seen in all treatment arms in the daily and once-monthly groups. It was confirmed that all once-monthly regimens were at least as effective as daily treatment. Substantial increases in total hip, femoral neck, and trochanter BMD were seen and the dose of 150 mg produced the most pronounced effect ($P<.05$ vs daily treatment). Independent of the regimen, most subjects (70.5%–93.5%) achieved increases above baseline in lumbar spine or total hip BMD or both.[35] This medication is also available as an IV formulation and can be used when oral bisphosphonates are not well tolerated. In the DIVA study, the optimal ibandronate IV injection schedule for the treatment of postmenopausal osteoporosis was studied, comparing the efficacy and tolerability of 2-monthly and 3-monthly injections with the previously evaluated daily oral ibandronate regimen.[36] Postmenopausal women aged 55 to 80 years old with osteoporosis (mean lumbar spine BMD T-score <-2.5 or worse) were included. At 2 years, the 2-monthly and 3-monthly IV regimens achieved statistical noninferiority but also superior increases in lumbar spine BMD compared with the daily regimen. Greater increases were also obtained with IV ibandronate versus daily oral in proximal femur BMD.[36]

In a large randomized controlled trial HORIZON-PFT means Health Outcomes and Reduced Incidence with Zoledronic Acid-Pivotal Fracture Trial Once Yearly in women with low BMD or with vertebral fractures, or both, a once per year infusion of zoledronic acid 5 mg resulted in significantly lower rates of vertebral fractures (by 70%), hip fractures (by 41%), and nonvertebral fractures (by 25%).[37] Because zoledronic acid can cause an acute-phase reaction (flulike symptoms up to 3 days after infusion), coadministration of acetaminophen may be used to reduce the incidence and severity of these side effects.[38] In the meta-analysis of Minyan and colleagues,[39] zoledronic acid was shown to be effective in the prevention of vertebral and nonvertebral fractures, as well as in increasing the BMD.

In terms of biological agents, denosumab was the first such therapy introduced for osteoporosis treatment. It is a fully human monoclonal RANKL antibody. It prevents

binding of RANKL to RANK, leading to inhibition of osteoclast activation. In the Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months (FREEDOM) trial, postmenopausal women aged 60 to 90 years old with a lumbar spine or total hip BMD T-score less than −2.5 but no less than −4.0 at the lumbar spine or total hip were randomized to receive placebo or denosumab 60 mg, administered subcutaneously every 6 months. Denosumab significantly reduced vertebral fractures, hip fractures, and nonvertebral fractures, with a cumulative incidence of 2.3% in the denosumab group versus 7.2% in the placebo group (relative risk 0.32) for vertebral fractures. In terms of risk of hip fracture, the denosumab group demonstrated a cumulative incidence of 0.7% versus 1.2% in the placebo group. For nonvertebral fractures, the cumulative incidence for denosumab treatment was 6.5% versus 8.0% in the placebo group.[40] In the FREEDOM extension trial, the effects of denosumab on bone mass over the long term were studied. This study captured up to 8 years of denosumab exposure for women who received 3 years of denosumab in FREEDOM and then continued in the extension (long-term group), and up to 5 years of denosumab exposure for women who received 3 years of placebo in FREEDOM and then transitioned to denosumab in the extension (crossover group). In the long-term group, mean BMD continued to increase for cumulative 8-year gains of 18.4% and 8.3% at the lumbar spine and total hip, respectively. In the crossover group, the mean BMD increased significantly from the extension baseline for 5-year cumulative gains of 13.1% and 6.2% at the lumbar spine and total hip, respectively. The yearly incidence of new vertebral and nonvertebral fractures remained low in both groups. Denosumab treatment lasting up to 8 years was associated with continued BMD gains, low fracture incidence, and a consistent safety profile.[41]

Miller and colleagues [42] assessed the long-term efficacy and the effects of discontinuing and restarting denosumab in postmenopausal women with low bone mass. They observed that the effects on bone turnover were fully reversible with discontinuation of denosumab and later restored after retreatment. There is a possibility of that denosumab in combination with other biologics agents could increase the risk for infections because RANK-RANKL are members of the tumor necrosis factor (TNF)/TNF receptor superfamily.

In the anabolic family of medications, teriparatide can be found, which is a PTH analogue.[43] It is the first anabolic medication approved to treat osteoporosis. Continuous PTH has catabolic effects, whereas daily intermittent PTH has anabolic skeletal effects.[44] Teriparatide was studied in women with previous vertebral fractures. It was associated with decreased vertebral and nonvertebral fractures as compared with placebo.[45] Teriparatide is useful in reducing vertebral fractures risk in patients with prior vertebral fractures. It can also be used in patients with severe osteoporosis in whom rapid bone growth is needed. Following a course of teriparatide, which can be given for a maximum of 2 years as recommended by the NOF, antiresorptives should be used to preserve or increase gain in BMD acquired by teriparatide.[46] Sequential treatment with teriparatide and denosumab resulted in a greater increase in BMD compared with switching of therapy.[47]

Combination treatments have been explored in clinical trials. Most recently, Cosman and colleagues[48] showed that a single infusion of zoledronic acid in combination with daily teriparatide for 1 year increased lumbar spine and total hip BMD by 7.5% and 2.3%, respectively, whereas zoledronic acid alone resulted in increases of 4.4% and 2.2%, respectively, and teriparatide alone provided increases of 7.0% and 1.1%, respectively. This shows that the combination of teriparatide and zoledronic acid gives the best results with significant increase of hip BMD seen in zoledronic acid and significant increase in spine BMD seen with teriparatide.

The combination of denosumab and teriparatide seems to have more of an additive effect.[47] Caution is necessary given that none of the studies have been designed to analyze the antifracture efficacy.

Most recently Kendler and colleagues[49] studied the effects of 24 months of treatment with teriparatide compared with risedronate on the incidence of new fractures in postmenopausal women with previous vertebral fractures, regardless of previous treatment. This was a double-dummy, active-controlled, head-to-head study designed to compare the effects of 2 osteoporosis drugs (teriparatide vs risedronate) targeting new vertebral fractures as the primary outcome. About 57.9% of the subjects were previously treated with bisphosphonates. A total of 31 women had an incident clinical vertebral fracture over 24 months. Of these, 7 were in the teriparatide group compared with 24 in the risedronate group. In the teriparatide group, incidence rate was 0.58; in the risedronate group, incidence rate was 1.97 events or patient-years ($P = .004$). Teriparatide was better at preventing fractures in subjects with severe osteoporosis compared with bisphosphonates, reducing by 71% the risk of new clinical vertebral fracture compared with risedronate.

The main reasons to consider a drug holiday and limit the use of bisphosphonates are possible adverse effects such as osteonecrosis of the jaw and atypical femoral fractures. Osteonecrosis of the jaw is defined as the presence of exposed and necrotic bone in the maxillofacial bone that does not heal within 8 weeks. In patients who may undergo invasive dental procedures, mainly tooth extractions, bisphosphonates may increase the risk of osteonecrosis of the jaw. Recently, it has been described that the patients at highest risk of developing this complication are those with malignancy-related skeletal conditions receiving high doses of IV bisphosphonates. The risk is proportional to the duration and cumulative dose of bisphosphonates; it is very rare, and the estimated incidence rate is less than 1:10,000 patient-years.[50] A recent review suggests that before major invasive dental surgery consideration should be given to stopping bisphosphonate therapy. It seems that good dental hygiene reduces the risk.[51]

Another feared complication is atypical femur fractures. In all case controlled randomized trials and cohort studies that have studied the relationship of atypical femur fracture and bisphosphonate treatment, the incidence of these fractures remains low.[52,53] There seems to be an increased risk after more than 5 years of bisphosphonate use.[54] Numerically, these fractures account for 4 to 5 of every 1000 femur fractures reported.[53]

A major criterion for atypical femur fractures is a fracture below the lesser trochanter of the femur. The main prodromal symptom is unilateral or bilateral dull or aching pain in the groin or thigh. A cohort study in Kaiser, California, examined 142 atypical fractures and found that 128 of those subjects were on bisphosphonates; this was observed 1 to 2 years into treatment, and the incidence was 1.8 per 100,000 per patient-year. After more than 8 years, the incidence increased to 113 per 100,000 per patient-year.[55] The incidence of typical femur fractures (femoral neck and trochanteric fractures) is 750 to 833 per 100,000 per patient-year after 8 years of treatment. For evaluation of suspected atypical femoral fracture, radiograph, bone scan, or MRI is indicated. It is important to be aware that 25% of the cases involve bilateral hips. In some case reports, patients with atypical femur fractures have been treated with teriparatide.[56]

Studies of bisphosphonates and the risk of atypical femur fractures with bisphosphonate use at 3 years have described a relative risk of 47.3 with both alendronate and risedronate.[57] After discontinuing any of the bisphosphonates for 1 year, the relative risk of fracture decreases significantly to 3.5.

Therefore, the physician must carefully consider the risk of hip fracture compared with the benefits and risks of bisphosphonates. For example, it has been argued that a patient with a T-score of −3.0 and a vertebral fracture in the last 2 years may not be an optimal candidate for discontinuation of therapy.[58,59]

Bisphosphonates may have a long-term residual effect on bone mass. Rodan and colleagues[60] described that, after 10 years of alendronate therapy and during a drug holiday, the medication will continue to be detectable levels. This finding raises the question about which patients will continue to have a benefit during greater than 5 years of bisphosphonate treatment. In the Fracture Intervention Trial Long-Term Extension (FLEX), subjects were randomized to alendronate, 5 mg/d, 10 mg/d, or placebo. After 5 years of treatment, the cumulative risk of nonvertebral fractures was not significantly different between those continuing (19%) and discontinuing (18.9%) alendronate. Among those who continued, there was a significantly lower risk of clinically recognized vertebral fractures (5.3% for placebo and 2.4% for alendronate); however, there was no significant reduction in morphometric vertebral fractures, which are fractures seen radiologically (11.3% for placebo and 9.8% for alendronate).[58] Bauer and colleagues[61] studied methods of predicting fracture risk in the FLEX study among women who have discontinued alendronate after 5 years. During 5 years of placebo, 94 of 437 women (22%) experienced 1 or more symptomatic fractures and 82 had fractures after 1 year. The 1-year changes in hip DXA were not related to subsequent fracture risk; however, older age and lower hip DXA at time of discontinuation were significantly related to increased fracture risk (total hip DXA relative hazard ratio, 1.87). In a post hoc analysis of FLEX, Schwartz and colleagues[62] evaluated postmenopausal women originally randomized to alendronate in the FIT trial who were treated for 5 years. Subjects were randomized to placebo (40%), alendronate 5 mg/d (30%), or alendronate 10 mg/d (30%) for an additional 5 years. Among women without vertebral fracture at the FLEX trial baseline, continuation of alendronate reduced nonvertebral fractures in women with femoral neck T-scores of −2.5 or worse but not with T-scores greater than −2.5 or better. Continuing alendronate for 10 years, instead of stopping after 5 years, reduces nonvertebral risk in women without prevalent vertebral fracture whose femoral neck T-scores after 5 years of alendronate are −2.5 or worse but does not reduce risk of nonvertebral fracture in women whose T-scores are −2 or better.

In the HORIZON-PFT extension trial, zoledronic acid at 6 years was compared with zoledronic acid at 3 years. In this study, postmenopausal women who received zoledronic acid for 3 years in HORIZON were randomized to 3 additional years of zoledronic acid or placebo. The primary endpoint was femoral neck BMD percentage change from year 3 to 6 in the intend-to-treat population. In years 3 to 6, femoral neck BMD remained constant in the zoledronic acid group and dropped slightly in the placebo group (but nevertheless remained greater than pretreatment levels). Other BMD sites showed similar differences. New vertebral fractures were lower in the zoledronic acid group at 6 years versus placebo, whereas other fractures were not different. In conclusion, this study demonstrated that fracture reductions suggest that those at high fracture risk, particularly for vertebral fracture, may benefit from continued treatment.[59,63] Subsequently, Black and colleagues[59] studied a second extension to 9 years of zoledronic acid in the HORIZON-PFT. In this study, women on zoledronic acid for 6 years in the first extension were randomized to either zoledronic acid or placebo for 3 additional years. The primary endpoint was change in total hip BMD at year 9 versus placebo. From years 6 to 9, the mean change in total hip BMD was −0.54% in the 3 additional years of zoledronic acid versus −1.31% in placebo group. The number of fractures was low and did not significantly differ by

treatment. The results suggest almost all patients who have received 6 annual zoledronic acid infusions can stop medication for up to 3 years with apparent maintenance of benefits. A post hoc analysis by Cosman and colleagues,[64] using HORIZON trial data, sought to define significant predictors of fracture and attempted to quantify fracture incidence in risk factor–defined subgroups of women who discontinued zoledronic acid after 3 years of treatment. Fracture risk after 6 years of zoledronic acid versus 3 years of zoledronic acid versus placebo was studied. They showed that subjects with a T-score of -2.5 or worse were more likely to have morphometric vertebral fractures on placebo versus zoledronic acid. After 3 years of zoledronic acid (in women with a total hip T-score >-2.5, no recent incident fracture, and no more than one risk factor), the risk for subsequent fracture over 3 additional years remained low for morphometric vertebral fracture if treatment was discontinued (vertebral fracture, average risk 3.2%; for nonvertebral fracture, average risk 5.8%). In these patients, discontinuation for up to 3 years is, therefore, reasonable. No difference for subjects with osteopenia was observed concerning the incidence of vertebral fractures, implying that this population can safely undergo a drug holiday.

In another post hoc analysis, Reid and colleagues[65] analyzed subjects from the HORIZON-PFT trial. They observed that the rate of reduction in fracture after 1 year of zoledronic acid compared with 3 years of zoledronic acid uncovered a 32% reduction in clinical fracture as compared with 34% in 3 years. Because this study suggests no significant difference of fracture risk reduction at 1 year and 3 years, a single infusion of zoledronic acid may be sufficient to reduce the risk of fracture. Larger studies will be needed to confirm this finding.

Black and colleagues[21] concluded that patients with low BMD at the femoral neck (T-score ≤ -2.5) despite 3 to 5 years of treatment are at highest risk for vertebral fractures and, therefore, seem to benefit most from continuation of bisphosphonates. Patients with an existing vertebral fracture who have a T-score of -2.0 may also benefit from continued therapy. Patients with a femoral neck T-score greater than -2.0 have a low risk of vertebral fracture and are unlikely to benefit from continued treatment.[21] Certainly these recommendations may change with further study.

This review of the literature suggests that a rational therapeutic approach should include assessment if treatment with oral bisphosphonates is needed for more than 5 years in patients who have a low hip T-score of less or equal to -2.5 at 5 years of alendronate therapy and at 3 years of zoledronate therapy. Extension of treatment in patients 75 years old or older, who have a history of vertebral fractures during therapy, may require specialty consultation.[21]

During a drug holiday, patients may be reassessed every 2 to 3 years by DXA. Therapy can be restarted in patients who have a new clinical fracture. However, it is possible that a drug holiday may be longer for patients exposed to zoledronic acid or alendronate as compared with risedronate or ibandronate due to differences in bone binding affinity of the medications.

In the recent years, and owing to new advances in knowledge of bone biology, new therapies have emerged, specific to different pathways of the bone-remodeling schema. Abaloparatide is a human recombinant-related PTH hormone, which is given by daily subcutaneous injection. This medication binds to the PTH-1 receptor, resulting in lower bone resorption, less hypercalcemia, and less cortical porosity.[66] Leder and colleagues[66] studied abaloparatide, comparing it with teriparatide and placebo in postmenopausal women. As compared with placebo, 24 weeks of daily subcutaneous abaloparatide increases BMD of the lumbar spine, femoral neck, and total hip in a dose-dependent fashion. Abaloparatide-associated increases in BMD at the total hip are greater than with teriparatide. Hypercalcemia in a 4-hour infusion was less. Also,

active trials comparing abaloparatide to teriparatide have shown no significant difference between the 2 medications in terms of nonvertebral and vertebral fractures. Results of the phase 3 pivotal fracture trial with abaloparatide were recently presented. In more than 18 months of treatment with abaloparatide and teriparatide, the incidence of vertebral fracture was decreased by 86% and 80%, respectively, compared with placebo. A significant 43% reduction in nonvertebral fracture risk was observed with abaloparatide. The difference in nonvertebral risk reduction between abaloparatide and teriparatide was not significant.

Other medications receiving attention in the past year are the humanized monoclonal antibodies against sclerostin, romosozumab, and blosozumab, which decrease bone resorption. In a phase 2 trial of postmenopausal women, romosozumab was found to be superior to teriparatide and alendronate in increasing BMD in the spine, total hip, and femoral neck.[67] Increase in bone mass density was 11.3% for romosozumab compared with teriparatide (7%) and alendronate (4%). When the drug is discontinued, there is a rapid decline in BMD.

In a multicenter, randomized, double-blind, placebo-controlled study of postmenopausal women with osteoporosis (BMD T-score <-2.5 at the total hip or femoral neck), subjects were randomized to subcutaneous placebo or romosozumab monthly for 12 months, followed by subcutaneous denosumab every 6 months for 12 months in both groups. They were able to demonstrate that at 12 months romosozumab reduced new vertebral fracture, with a relative risk reduction of 73%. At 1 year, those subjects who received romosozumab, and after transition to denosumab, had persistent vertebral fracture risk reduction lasting through month 24. The conclusion was that romosozumab 210 mg monthly reduced vertebral and clinical fracture risk versus placebo at month 12 and vertebral fracture risk reduction through month 24 after transitioning to denosumab in both groups. The sequence of romosozumab followed by denosumab is highly effective and well-tolerated.[68]

Most importantly, a new study has effectively compared romosozumab head-to-head with bisphosphonates. Saag and colleagues[69] performed a multicenter double-blind study with postmenopausal women with osteoporosis and high fracture risk. Subjects were randomized to receive romosozumab 210 mg monthly or alendronate 70 mg weekly for 12 months, followed by open-label alendronate 70 mg weekly in both groups. The combination of romosozumab with alendronate reduced new vertebral, clinical, and nonvertebral hip fracture, with the greatest effect on reduction of new vertebral fracture and hip fracture (relative risk reduction 50% and 38%, respectively) alongside increase of BMD. This suggests that in patients with high risk for fractures, a treatment regimen starting with romosozumab followed by alendronate lead to better outcomes in terms of lower risk of fractures compared with alendronate monotherapy. As of the time of this article, this medication has not been approved by the FDA.

SUMMARY

Current approaches to the treatment of osteoporosis are based on BMD and fracture risk assessment. Bisphosphonates are typically the first-line agents. A treatment failure is considered when significant loss in BMD is seen or the patient sustains a fracture despite ongoing treatment. A drug holiday is considered after 3 to 5 years of bisphosphonate treatment. Goal-directed treatment has been recently proposed based on BMD or fracture risk assessment using the FRAX tool to aim for a reduction of fracture risk.[70] This new paradigm may help physicians to manage osteoporosis with the least potential for adverse effects.

REFERENCES

1. Center J, Nguyen TV, Schneider D, et al. Mortality after all major types of osteoporotic fracture in men and women: an observational study. Lancet 1999; 353(9156):878–82.
2. Silverman S, Christiansen C. Individualizing osteoporosis therapy. Osteoporos Int 2012;23:797–809.
3. Lin JT, Lane JM. Rehabilitation of the older adult with an osteoporosis-related fracture. Clin Geriatr Med 2006;22:435–47.
4. Rapp K, Rothenbacher D, Magaziner J, et al. Risk of nursing home admission after femoral fracture compared with stroke, myocardial infarction, and pneumonia. J Am Med Dir Assoc 2015;16(8):715.e7-12.
5. Solomon DH, Johnston SS, Boytsov NN, et al. Osteoporosis medication use after hip fracture in U.S. patients between 2002 and 2011. J Bone Miner Res 2014; 29(9):1929–37.
6. Kanis JA, McCloskey EV, Johansson E, et al. A reference standard for the description of osteoporosis. Bone 2008;42:467–75.
7. Khosla S. Minireview: the OPG/RANKL/RANK system. Endocrinology 2001; 142(12):5050–5.
8. Khosla S, Melton LJ, Riggs BL, et al. The unitary model for estrogen deficiency and the pathogenesis of osteoporosis: is a revision needed? J Bone Miner Res 2010;26(3):441–51.
9. Lim SY, Bolster MB. Current approaches to osteoporosis treatment. Curr Opin Rheumatol 2015;27(3):216–24.
10. Duque G, Troen BR. Understanding the mechanisms of senile osteoporosis: new facts for a major geriatric syndrome. J Am Geriatr Soc 2008;56(5):935–41.
11. Feldstein AC, Nichols G, Orwoll E, et al. The near absence of osteoporosis treatment in older men with fractures. Osteoporos Int 2005;16:953–62.
12. Kiebzak GM, Beinart GA, Perser K, et al. Undertreatment of osteoporosis in men with hip fractures. Arch Intern Med 2002;162:2217–22.
13. Abbasi AA, Rudman D, Wilson CR, et al. Observations on nursing home patient with history of hip fracture. Am J Med Sci 1995;310:229–34.
14. Ebeling P, Wark JD, Stella J, et al. Effects of calcitriol or calcium on bone mineral density, bone turnover, and fractures in men with primary osteoporosis: a two-year randomized, double blind, double placebo study. J Clin Endocrinol Metab 2001;86(9):4098–103.
15. Behre H, Kliesch S, Leifke E, et al. Long-term effect of testosterone therapy on bone mineral density in hypogonadal men. J Clin Endocrinol Metab 1997;82(8): 2386–90.
16. Cosman F, de Beur SJ, LeBoff MS, et al. Clinician's guide to prevention and treatment of osteoporosis. Osteoporos Int 2014;25:2359–81.
17. U.S. Preventive Services Task Force. Screening for osteoporosis: U.S. preventive services task force recommendation statement. Ann Intern Med 2011;154(5): 356–64.
18. Densitometry, N.O.F.a.I.S.f.C. Recommendations to DXA Manufacturers for FRAX® Implementation. Available at: www.nof.org/files/nof/public/content/resource/862/files/392.pdf. Accessed January 4, 2018.
19. Watts NB, Adler RA, Bilezikian JP, et al. Osteoporosis in men: an endocrine society clinical practice guideline. J Clin Endrocinol Metab 2012;97(6):1802–22.
20. Giangregorio LM, Leslie WD, Lix LM, et al. FRAX underestimates fracture risk in patients with diabetes. J Bone Miner Res 2011;27(2):301–8.

21. Black DM, Bauer DC, Schwartz AV, et al. Continuing bisphosphonate treatment for osteoporosis–for whom and for how long? N Engl J Med 2012;366(22):2051–3.
22. Hinton PS, Nigh P, Thyfault J, et al. Effectiveness of resistance training or jumping-exercise to increase bone mineral density in men with low bone mass: a 12-month randomized, clinical trial. Bone 2015;79:203–12.
23. Black DM, Rosen CJ. Postmenopausal osteoporosis. N Engl J Med 2016;374(3): 2096–7.
24. Murad MH, Drake MT, Mullan RJ, et al. Comparative effectiveness of drug treatments to prevent fragility fractures: a systemic review and network meta-analysis. J Clin Endrocinol Metab 2012;97:1871–80.
25. Jackson RD, LaCroix AZ, Gass M, et al. Calcium plus vitamin D supplementation and the risk of fractures. N Engl J Med 2006;354:669–83.
26. Amory JK, Watts NB, Easley KA, et al. Exogenous testosterone or testosterone with finasteride increases bone mineral density in older men with low serum testosterone. J Clin Endocrinol Metab 2004;89(2):503–10.
27. Ettinger B, Black DM, Mitlak B, et al. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3 year randomized clinical trial. Multiple outcomes of raloxifene evaluation (MORE) investigators. JAMA 1999;282(7):637–45.
28. Cummings SR, Tice JA, Bauer S, et al. Prevention of breast cancer in postmenopausal women: approaches to estimating and reducing risk. J Natl Cancer Inst 2009;101:384–98.
29. Black DM, Cummings SR, Karpf DB, et al. Randomized trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Fracture Intervention Trial Research Group. Lancet 1996;348:1535–41.
30. Cummings SR, Black DM, Thompson DE, et al. Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the fracture intervention trial. JAMA 1998;280:2077–82.
31. Harris ST, Watts NB, Genant HK, et al. Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. Vertebral Efficacy With Risedronate Therapy (VERT) Study Group. JAMA 1999;282:1344–52.
32. Reginster J, Minne HW, Sorensen OH, et al. Randomized trial of the effects of risedronate on vertebral fractures in women with established postmenopausal osteoporosis. Vertebral Efficacy with Risedronate Therapy (VERT) Study Group. Osteoporos Int 2000;11:83–91.
33. McClung MR, Geusens P, Miller PD, et al. Hip Intervention Program Study Group. Effect of risedronate on the risk of hip fracture in elderly women. Hip Intervention Program Study Group. N Engl J Med 2001;344:333–40.
34. Chestnut CH, Skag A, Christiansen C, et al. Oral Ibandronate Osteoporosis Vertebral Fracture Trial in North America and Europe (BONE). Effects of oral ibandronate administered daily or intermittently on fracture risk in postmenopausal osteoporosis. J Bone Miner Res 2004;19:1241–9.
35. Reginster JY, Adami S, Lakatos P, et al. Efficacy and tolerability of once-monthly oral ibandronate in postmenopausal osteoporosis: 2 year results from the MOBILE study. Ann Rheum Dis 2006;65(5):654.
36. Eisman JA, Civitelli R, Adami S, et al. Efficacy and tolerability of intravenous ibandronate injections in postmenopausal osteoporosis: 2-year results from the DIVA study. J Rheumatol 2008;35:488–97.
37. Black DM, Delmas PD, Eastell R, et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. N Engl J Med 2007;356(18):1809–22.

38. Reid IR, Gamble GD, Mesenbrink P, et al. Characterization of and risk factors for the acute-phase response after zolendronic acid. J Clin Endrocinol Metab 2010; 95:4380–7.
39. Minyan L, Guo L, Pei Y, et al. Efficacy of zoledronic acid in treatment of osteoporosis in men and women-a meta-analysis. Int J Clin Exp Med 2015;8(3):3855–61.
40. Reginster JY, Neuprez A, Dardenne N, et al. Efficacy and safety of currently marketed antiosteoporosis medications. Best Pract Res Clin Endocrinol Metab 2014; 28(809):809–34.
41. Papapoulos S, Lippuner K, Roux C, et al. The effect of 8 or 5 years of denosumab treatment in postmenopausal women with osteoporosis: results from the FREEDOM Extension study. Osteoporos Int 2015;26(12):2773.
42. Miller PD, Bolognese MA, Lewiecki M, et al. Effect of Denosumab on bone density and turnover in postmenopausal women with low bone mass after long-term continued, discontinued, and restarting of therapy: A randomized blinded phase 2 clinical trial. Bone 2008;43(2):222–9.
43. Watts NB, Roux C, Modlin JF, et al. Infections in postmenopausal women with osteoporosis treated with denosumab or placebo: coincidence or casual association? Osteoporos Int 2012;23:327–37.
44. Silva BC, Costa AG, Cusano NE, et al. Catabolic and anabolic actions of parathyroid hormone on the skeleton. J Endocrinol Invest 2011;34:801–10.
45. Neer RM, Arnaud CD, Zanchetta JR, et al. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. N Engl J Med 2001;344:1434–41.
46. Black DM, Bilezikian JP, Ensrud KE, et al. One year of alendronate after one year of parathyroid hormone (1-84) for osteoporosis. N Engl J Med 2005;353:555–65.
47. Leder BZ, Tsai JN, Uihlein A, et al. Denosumab and teriparatide transitions in postmenopausal osteoporosis (the DATA-Switch study): extension of a randomised controlled trial. Lancet 2015;386(9999):1147.
48. Cosman F, Eriksen EF, Recknor C, et al. Effects of intravenous zoledronic acid plus subcutaneous teriparatide [rhPTH (1,34)] in postmenopausal osteoporosis. J Bone Miner Res 2011;26:503–11.
49. Kendler DL, Marin F, Zerbini CA, et al. Effects of teriparatide and risedronate on new fractures in post-menopausal women with severe osteoporosis (VERO): a multicenter, double-blind, double-dummy, randomized controlled trial. Lancet 2017 [pii:S0140-6736(17)32137-2].
50. Suresh E, Pazianas M, Abrahamsen B, et al. Safety issues with biphosphonate therapy for osteoporosis. Rheumatology 2014;53:19–31.
51. Khan AA, Morrison A, Hanley DA, et al. Diagnosis and management of osteonecrosis of the jaw: a systematic review and international consensus. J Bone Miner Res 2015;30:3–23.
52. Schilcher J, Koeppen V, Aspenberg P, et al. Risk of atypical femoral fracture during and after bisphosphonate use. N Engl J Med 2014;371:974–6.
53. Feldstein AC, Black D, Perrin N, et al. Incidence and demography of femur fractures with and without atypical features. J Bone Miner Res 2012;27:977–86.
54. Favus MJ. Bisphosphonates for osteoporosis. N Engl J Med 2010;363(21): 2027–35.
55. Dell RM, Adams AL, Greene DF, et al. Incidence of atypical nontraumatic diaphyseal fractures of the femur. J Bone Miner Res 2012;27(12):2544–50.
56. Im GI, Lee SH. Effect of teriparatide on healing of atypical femoral fractures: a systemic review. J Bone Metab 2015;22(4):183–9.

57. Schilcher J, Michaëlsson K, Aspenberg P, et al. Bisphosphonate use and atypical fractures of the femoral shaft. N Engl J Med 2011;364(18):1728–37.
58. Black DM, Schwartz AV, Ensrud KA, et al. Effects of continuing or stopping alendronate after 5 years of treatment the Fracture Intervention Trial Long-Term Extension (FLEX): a randomized trial. JAMA 2006;296(24):2927–38.
59. Black DM, Reid IR, Cauley JA, et al. The effect of 6 versus 9 years of zoledronic acid treatment in osteoporosis: a randomized second extension to the HORIZON-Pivotal Fracture Trial (PFT). J Bone Miner Res 2015;30(5):934–44.
60. Rodan G, Reszka A, Golub E, et al. Bone safety of long-term bisphosphonate treatment. Curr Med Res Opin 2004;20(8):1291.
61. Bauer DC, Schwartz A, Palermo L, et al. Fracture prediction after discontinuation of 4 to 5 years of alendronate therapy: the FLEX study. JAMA Intern Med 2014; 174(7):1126–34.
62. Schwartz AV, Bauer DC, Cummings SR, et al. Efficacy of continued alendronate for fractures in women with and without prevalent vertebral fracture: the FLEX trial. J Bone Miner Res 2010;25(5):976–82.
63. Black DM, Reid IR, Boonen S, et al. The effect of 3 versus 6 years of zoledronic acid treatment of osteoporosis: a randomized extension to the HORIZON-Pivotal Fracture Trial (PFT). J Bone Miner Res 2012;27(2):243–54.
64. Cosman F, Cauley JA, Eastell R, et al. Reassessment of fracture risk in women after 3 years of treatment with zoledronic acid: when is it reasonable to discontinue treatment? J Clin Endrocinol Metab 2015;99(12):4546–54.
65. Reid IR, Black DM, Eastell R. Reduction in the risk of clinical fractures after a single dose of zoledronic acid 5 milligrams. J Clin Endrocinol Metab 2013;98(2): 557–63.
66. Leder BZ, O'Dea LS, Zanchetta JR, et al. Effects of abaloparatide, a human parathyroid hormone-related peptide analog, on bone mineral density in postmenopausal women with osteoporosis. J Clin Endrocinol Metab 2015;100(2):697–706.
67. McClung ML, Grauer A, Boonen S, et al. Romosozumab in postmenopausal women with low bone mineral density. N Engl J Med 2014;370(5):412–20.
68. Cosman F, Crittenden DB, Adachi JD, et al. Romosozumab treatment in postmenopausal women with osteoporosis. N Engl J Med 2016;(375):1532–43.
69. Saag KG, Petersen J, Brandi ML, et al. Romosozumab or alendronate for fracture prevention in women with osteoporosis. N Engl J Med 2017;377:1417–27.
70. Cummings SR, Cosman F, Eastell R, et al. Goal-directed treatment of osteoporosis. J Bone Miner Res 2013;28:433–8.

Regional Rheumatic Disorders and Rehabilitation in Older Adults: An Update

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KEYWORDS

- Regional rheumatic pain syndromes • Geriatric rehabilitation
- Rehabilitation medicine

KEY POINTS

- To review key components of the rehabilitation medicine evaluation of older patients with regional rheumatic disorders.
- To understand the rationale behind rehabilitation medicine treatment interventions of older patients with regional rheumatic disorders.
- To review future research considerations of older patients with regional rheumatic disorders.

INTRODUCTION

Musculoskeletal (MSK) problems are the most frequently reported complaints among community-dwelling older adults.[1,2] In patients more than 60 years old, the prevalence of pain was more than 2 times that reported for patients less than 60 year old.[3,4] In developed countries, the fastest growing portion of the population are individuals who are older than 75 years of age.[4,5] The impact of the aging process on skeletal muscles and joints can have a profound effect on the functional ability of individuals with and without disabilities.[6] Despite its universal occurrence, the mechanisms of aging are not fully understood.[7,8] Structural and mechanical changes of aging occur in skeletal muscle and the articular cartilage, resulting in biomechanical changes that affect mobility, self-care skills, and activities of daily living (ADLs). This article reviews the rehabilitation medicine approach to the evaluation of older adults with regional rheumatic disorders and the approach to clinical intervention.

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WHAT IS A REGIONAL RHEUMATIC DISORDER?

For the purposes of this article, a regional rheumatic disorder is a localized dysfunction related to nonarticular or periarticular soft tissue. The disorder may involve the bursa, muscle, fascia, ligament, tendon, cartilage, joint, bone, nerve, or overlying skin and how these tissues relate to each other.[9] Local trauma is the most common initiating event for regional rheumatic disorders. A macrotraumatic injury involves a single episode of acute tissue destruction, whereas a microtraumatic injury can result from chronic overload or repetitive overuse.[10] Intrinsic and extrinsic factors affect these injuries and predispose to inflammation, degeneration, tear, or rupture.[10] Examples of intrinsic factors include age-related changes, biomechanical malalignment, muscle imbalance, hypermobility or hypomobility, poor vascular supply,[10] undermobility and lack of exercise, and comorbidities. Tendons become less flexible and elastic with aging, making them more susceptible to injuries.[11] Extrinsic factors relate to external environmental issues that may affect individuals, such as uneven walking surfaces, tripping hazards, lack of accessibility in the home, lack of access to exercise opportunities, poor exercise training techniques, exposure to extreme temperature fluctuations, and/or financial barriers to exercise/environmental modifications.

PATIENT EVALUATION CONSIDERATIONS

Given the absence of specific standardized laboratory tests, markers, or imaging tests for regional rheumatic disorders, a comprehensive medical history and physical examination are essential. The initial medical history should differentiate whether the complaint is articular or nonarticular, inflammatory or noninflammatory, acute or chronic, and localized or widespread.[9]

Pain is often the primary symptom in patients with MSK complaints. Critical elements of a pain history include pain onset, location, duration, type of pain, and associated factors that may aggravate, exacerbate, or decrease pain. Clinicians should query patients for a history of recent or remote trauma. Associated symptoms, such as weakness, edema, effusion, redness, warmth, fevers, and chills, are important in the differential diagnosis.

REHABILITATION MEDICINE HISTORY

A comprehensive functional history is critical for identifying activities that may be related to symptoms of regional rheumatic disorders. This includes an understanding of the premorbid level of functioning, which includes inquiring about ADLs and mobility in the home and community. Mobility tasks include transfers, walking, curbs, stairs, driving, use of mobility aids (canes, walkers, or wheelchairs), and avocational activities. Inquiring about a patient's level of function (independent, required assistance, or dependent) prior to an MSK complaint is also important to document. ADL history includes self-care skills in the areas of bathing, toileting, personal hygiene, upper and lower limb dressing, meal preparation, home maintenance/laundry. The inability to put on deodorant or a shirt because of restricted shoulder range of motion in the case of a shoulder tendinopathy or rotator cuff tear is an example of how MSK problems can have an impact on ADL function.

In addition to gathering the traditional information, clinicians should consider some unique factors that influence the trajectory of older adults with regional rheumatic disorders from disease to disability (**Box 1**).[12–14]

Box 1
Additional factors to consider when gathering a patient's history

- Patient's/family's understanding of the disease and its implications
- Patient's/family's goals related to rehabilitation
- Cultural beliefs/behaviors (health beliefs)
- Role function
- Social support/interaction/activities
- Exercise likes and dislikes/frequency and intensity of regular activity
- Sexual activity
- Recreational hobbies
- Substance abuse
- Family/caregiver resources
- Methods of coping/adaptation to stress
- Values/spirituality
- Signs of elder abuse/mistreatment (be aware of the state's reporting requirements)

An important area to address during the systems review is cognition. Because the inability to learn can negatively affect the rehabilitation program, older adults should also be screened for the following[12]:

- Communication ability (eg, ability to make needs known)
- Affect (eg, expected emotional/behavioral responses)
- Cognition (eg, assessment of consciousness and orientation)
- Learning style/preferences (eg, learning barriers and education needs)

PHYSICAL EXAMINATION

A comprehensive physical examination should include inspection; palpation; passive and active range of motions of the joints; and documenting muscle tone, atrophy, and strength, sensation, and proprioception. It is imperative to evaluate for physical asymmetries, postural abnormalities, joint deformities, muscle imbalances, and limb discrepancies that may have been preexisting or the result of an acute injury. In all patients with MSK disorders, an assessment of coordination and of static and dynamic balance testing should be included. The range-of-motion examination is particularly important, because even minor losses in range of motion can negatively affect function.[15] For example, loss of shoulder external rotation may result in the inability to wash hair. Loss of range of motion at the wrists and fingers may affect any activities requiring manual dexterity.[15] Decreased hip rotation and extension may have a negative impact on gait efficiency,[15] which may worsen in a clinical scenario of trochanteric bursitis. **Table 1** highlights unique factors that should be considered during the physical examination of older adults with regional rheumatic disorders. Many older patients present with combinations of MSK and neurologic impairments (weakness, sensory loss, and balance issues) as well as medical comorbidities (cardiac and pulmonary). The functional impact of multisystem impairments and comorbidities is likely to be greater than that seen in patients with isolated MSK impairments.

Table 1
Special considerations when selecting tests and measures for older adults with regional rheumatic disorders

ROM	Joint pain or activity tolerance may prevent traditional goniometric ROM testing. Functional ROM testing may be substituted to determine whether the older adult has the range needed to perform self-care activities.[16]
Strength	Pain and joint effusion impede muscle contraction, thus limiting the examination of strength. Traditional strength testing (eg, MMT) is not appropriate in the presence of severely deformed joints. Functional strength assessments provide sufficient data to formulate treatment goals and assess outcomes.[16]
Joint mobility	With aging, connective tissue can lose elastic properties, causing increased or decreased joint mobility. Systemic conditions, such as diabetes and rheumatoid arthritis, are associated with impairments in joint mobility.[17]
Sensory integrity	Alterations in sensation may be evident with the presence of Raynaud disease, compression of nerves because of inflammation or joint derangement, diabetes, or normal age-related changes.[16]
Cardiovascular	Heart rate, respiratory rate, blood pressure, and RPE should all be measured. Be aware of medications that may blunt heart rate or blood pressure response to exercise. Excessive increases in RPE may indicate the presence of inflammation or impairment of pulmonary and cardiac function that requires more extensive and formal evaluation.[16]
Functional assessment	A suggested first step is observational analysis of functional tasks. Considering the lack of established reliability, however, observational task analysis should be used cautiously. Rather than being used independently, observational task analysis should guide the selection of additional quantitative tests and measures. The quantification of functional activity, if based on valid and reliable measures, allows clinicians to describe patient/client progression and document outcomes.[17]

Abbreviations: MMT, manual muscle testing; ROM, range of motion; RPE, ratings of perceived exertion.

Data from Vlieland TPV. Multidisciplinary team care and outcomes in rheumatoid arthritis. Curr Opin Rheumatol 2004;16(2):153–6; and Federal Interagency Forum on Aging-Related Statistics. Older Americans 2012: key indicators of well-being. Washington, DC: US Government Printing Office; 2012.

SUPPLEMENTARY WORK-UP

The findings on physical examination guide additional work-up, which may include laboratory and/or imaging studies. A full discussion of either of these topics is beyond the scope of this article. Ultrasonography (US) imaging is reviewed in this article, because this imaging technique is commonly used by physiatrists and has become an extension of the physical examination.[18–20]

Brightness mode (B-mode) US is widely used in clinical practice for assessment of the MSK system, including muscles, tendons, joints, ligaments, and neurovascular structures. The development of high-frequency linear US transducers has revolutionized MSK imaging and produces exquisitely detailed high-resolution images and has revolutionized the imaging of many MSK structures (**Fig. 1**). US can reveal the presence of anatomic variations and disorders, including tendinopathy, tendon tears/ruptures, ligament laxity/tears, joint effusions, bursal enlargement, and muscle diseases/injury/atrophy involving MSK structures[21] (**Fig. 2**).

Advantages of US imaging include its portability, the absence of ionizing radiation, accessibility, and lower cost compared with MRI or CT. Another advantage of US is

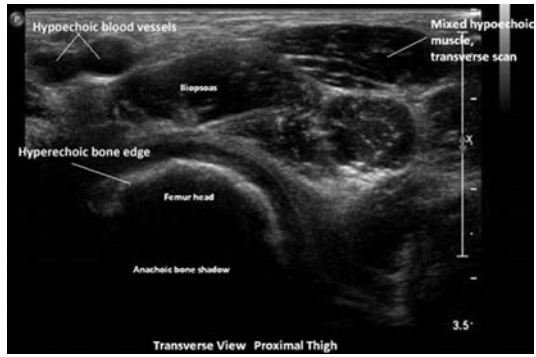

Fig. 1. Transverse B-mode US image—hip.

that it can be used during dynamic assessment of patients. Examples include evaluation of impingement while moving a shoulder through its range of motion, abnormal ligamentous laxity when a joint is mechanically stressed, and sonopalpation of the area of interest (using a transducer to recreate pain or observe the effects of compression). Color Doppler US is also useful for imaging the MSK system and may reveal hypervascularity or increased blood flow in areas of inflammation or neovascularization.[21,22]

US is also useful for procedural guidance, including joint aspiration; injections of joints, tendons, and ligaments; and US-guided needle tenotomy (**Fig. 3**).

COMMON REGIONAL RHEUMATIC PAIN SYNDROMES

The rheumatology and physical medicine literature describing regional rheumatic syndrome is extensive. The authors encourage readers to review the listed references.[11,23–27]

Bursae Disorders

Briefly, most bursae disorders are inflammatory, hence the term, *bursitis*. The function of the bursa is to facilitate movement of tendons and muscles over bony

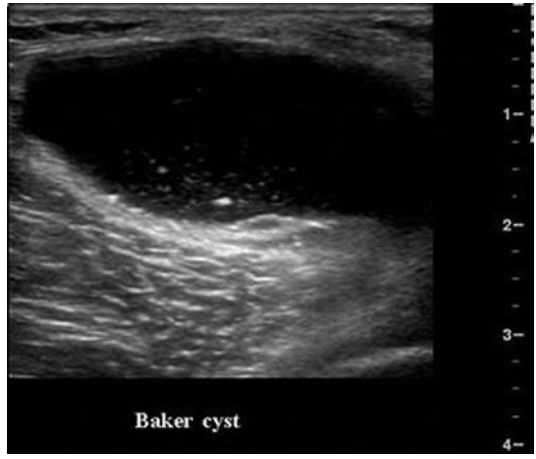

Fig. 2. B-mode US image—Baker cyst.

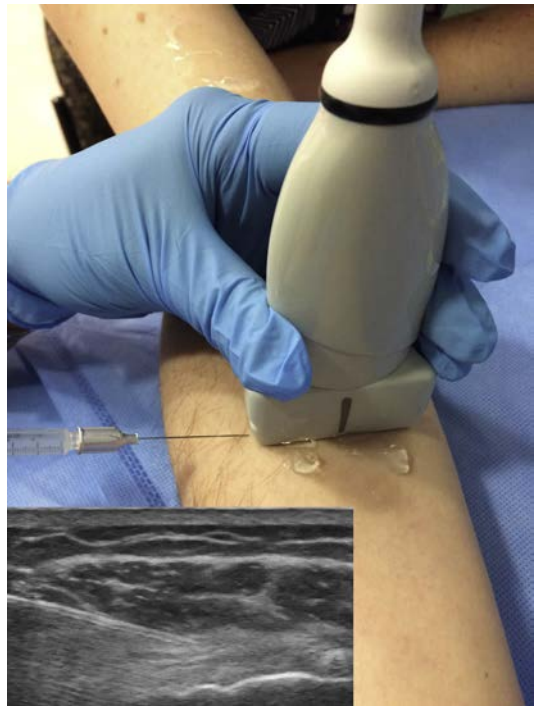

Fig. 3. In-plane needle insertion, forearm.

prominences.[28] Both excessive and repetitive motions from overuse, trauma, systemic disease, or infection may cause bursitis.[28] **Box 2** lists common types of bursitis in the clinical setting.

The medical treatment of most bursitis is straightforward and involves rest, identifying and preventing the aggravating factors, the use of nonsteroidal oral anti-inflammatory agents (unless medically contraindicated), and/or the administration of a glucocorticoid injection. Glucocorticoid injections may be diagnostic as well as curative.

Box 2
Common bursitis in the clinical setting

- Subacromial bursitis/subdeltoid bursitis of the shoulder
- Olecranon bursitis over the posterior elbow
- de Quervain tenosynovitis of the wrist
- Trochanteric bursitis of the hip
- Ischial bursitis (weaver's bottom)
- Iliopsoas bursitis
- Prepatellar bursitis of the knee (housemaid's knee)
- Anserine bursitis
- Achilles bursitis/retrocalcaneal bursitis

Injuries present with localized pain and tenderness. Clinicians should differentiate acute degeneration (inflammation tendinitis) versus chronic degeneration (tendinopathy) because treatment goals and healing times differ.

Ligamentous Injuries

Ligamentous injuries may result in sprains, which may be graded according to the degree of severity.

- Grade I injury: ligament is overstretched, without joint instability
- Grade II injury: ligament is partially torn; there is mild joint instability.
- Grade III injury: ligament is completely torn; there is joint instability and significant bruising.

Muscle or Tendon Injuries

Muscle or tendon injuries may result in strains, which are also graded per severity.

- Grade I injury: muscle or tendon tissue is overstretched.
- Grade II injury: muscle or tendon tissue is partially torn.
- Grade III injury muscle or tendon tissue is completely torn.

Most strains present with swelling, bruising, pain, local warmth, and/or local nodule or point tenderness and dysfunction. Complete tears are suspected in cases of weakness and complete disruption of movement. In cases of severe disruption and instability, a secondary nerve impingement may occur. **Box 3** lists common tendinopathies in the clinical setting.

Tendinopathies (wear and tear injuries) are much more common that tendonitis (inflammation of tendons). The presence of tendinopathy versus tendonitis can be suspected by a patient's history (chronic, gradual onset of pain) and lack of signs of inflammation on clinical assessment and then confirmed on US imaging (B-mode or color Doppler).[21,23,24]

SPECIFIC TESTS

To differentiate the various entities and degree of injury, clinicians may rely on specific tests. For example, the drop-arm test requires an examiner to passively abduct a

Box 3
Common tendinopathies in the clinical setting

- Shoulder rotator cuff tendinopathy
- Shoulder rotator cuff tear (complete or incomplete)
- Proximal bicipital tendinitis/tendinopathy
- Adhesive capsulitis (frozen shoulder)
- Lateral elbow epicondylitis (tennis elbow)
- Medial elbow epicondylitis (golfer's elbow)
- Triceps tendon rupture
- Tenosynovitis of the wrist
- Popliteal tendinitis of the knee/tendinopathy
- Patellar tendinitis/tendinopathy
- Achilles tendinitis/tendinopathy
- Posterior tibialis tendon tendinitis or rupture

patient's shoulder 90°. The patient is then asked to slowly lower the arm back to the side. A positive test result is indicated by a patient's inability to voluntarily lower the arm in a smooth and continuous fashion and is highly suggestive of a complete rotator cuff tear.[23,24]

Multiple regional tests exist to determine the tissue injured and the level of apprehension or instability. Some of the most commonly used tests in the clinical setting are listed in **Table 2**.[23–25]

OUTCOME MEASURES

Clinicians are encouraged to consider the use of clinical outcome measures to establish objective data in each patient and to subsequently use that data to monitor treatment response.

For example, the Disabilities of the Arm, Shoulder and Hand (DASH) questionnaire is a 30-item questionnaire that assesses the ability of a patient to perform certain upper extremity activities.[29] It is a self-report questionnaire with which patients can rate difficulty and interference with daily life and self-care skills.

In addition to the DASH questionnaire, there are multiple practical, well-validated, and easy-to-administer outcome measures, such as the Functional Reach Test, the 6-Minute Walk Test, and the Timed Up-and-Go Test.

All these tests can be performed quickly in the clinical setting. They may provide invaluable information in monitoring treatment response and identifying needed rehabilitation and supporting resources for older adults.

Once a diagnosis is reached and a standard medical treatment plan delineated, the rehabilitation process can begin.

ADDRESSING AND DOCUMENTING THE NEED FOR PHYSICAL REHABILITATION

It is important to remember that older adults with regional rheumatic disorders may need additional care, beyond standard medical treatment, to achieve and maintain an optimal level of functioning. Many older adults have multiple comorbidities and

Table 2
Common special tests for regional rheumatic disorders

Body Region	Special Tests
Shoulder	• Speed test for biceps tendinitis • Yergason test for bicipital tendon instability • Neer-Walsh impingement test for rotator cuff tendinitis
Elbow	• Cozen test for lateral epicondylitis
Wrist and hand	• Finkelstein test for de Quervain tenosynovitis
Hip	• Thomas test • Ober test • Patrick test
Knees	• Lachman test • McMurray test • Valgus and varus stress test
Ankles	• Anterior drawer test • Thompson test

Data from O'Sullivan SB, Schmitz TJ, Fulk GD. Physical rehabilitation. Philadelphia: F.A. Davis Co; 2014; and Richards S, Cristian A. The role of the physical therapist in the care of the older adult. Clin Geriatr Med 2006;22(2):269–79.

may be affected by polypharmacy. Therefore, awareness and the use of nonpharmacologic therapies are crucial. Physical rehabilitation is an important adjunct to pharmacologic treatment in many patients.[17]

THE PHILOSOPHY OF PHYSICAL REHABILITATION

Maintaining functional independence is a key indicator of life satisfaction in older adults.[16] In physical rehabilitation, functioning represents both the starting point and the outcome of patient/client management. Traditional biomedical models of health care often focus solely on the diagnosis and treatment of underlying disease. In contrast, physical rehabilitation philosophy considers the biopsychosocial model of health care. The broad goal is to treat the whole person, rather than focus on a singular medical problem. Biological, psychological, and social factors all play important roles in human functioning. These factors account for the day-to-day variation in function of individuals as well as functional differences between individuals with similar disease severity.[30]

The World Health Organization International Classification of Function (ICF) (**Fig. 4**) is based on a biopsychosocial model providing clinicians with a unified, standard language and framework for capturing how an individual's health condition(s) function in daily life. Using the ICF terminology, health conditions cause impairments in body structure and function; these impairments may affect activity and ultimately participation.[31] Rehabilitation professionals are challenged to think holistically about patient care needs, including systematically identifying specific impairments, activity limitations, and participation restrictions, in conjunction with personal and environmental contextual factors.

GENERAL CONSIDERATIONS IN GERIATRIC REHABILITATION

Although the fundamental principles of physical rehabilitation are similar regardless of a patient's age, there are unique features and considerations in the management of older adults that can greatly improve outcomes.[32]

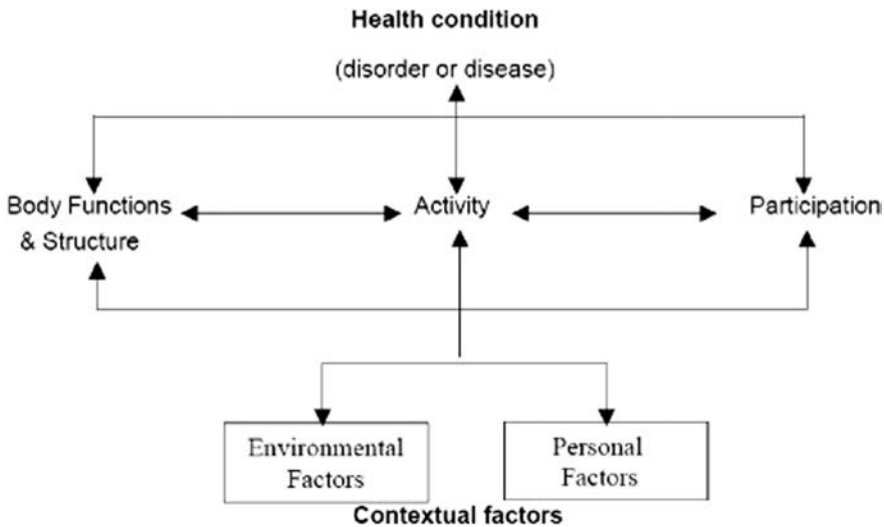

Fig. 4. ICF. (*From* WHO. Towards a common language for functioning, disability and health: ICF. Geneva (Switzerland): World Health Organization; 2002. p. 9; with permission.)

Aging Is a Heterogeneous Process

Older adults become increasingly dissimilar, which cannot be attributed to aging alone.[32] Understanding the heterogeneous nature of the older population is crucial to the success of any rehabilitation plan of care. Clinicians must keep in mind that stereotypical information, although helpful in understanding older people as a global population, may not fit any individual situation.[33,34]

Older Adults Commonly Have Multiple Chronic Conditions

More than two-thirds of older Americans have 2 or more chronic conditions and 14% have 6 or more.[30] Furthermore, acute illnesses can be superimposed on these chronic conditions, which makes rehabilitation management complex and challenging. Therefore, a multidisciplinary approach is important in the delivery of geriatric rehabilitative services. Multidisciplinary team management assists in ensuring that patients receive comprehensive evaluations and care for the primary health condition and all associated comorbidities.[31]

Older Adults Have Unique Psychosocial Needs

Adults face many different transitions throughout life. In the case of older adults, many of these transitions are characterized by physical, psychological, social, and economic loss. To provide successful rehabilitative services, clinicians must comprehensively consider the psychosocial factors that may influence (both positively and negatively) a client's participation in rehabilitation and then place the physical findings in the context of the older adult's psychosocial environment.

Physical Rehabilitation Efforts Should Focus on Function

Because maintaining functional independence is a key indicator of life satisfaction in older adults,[16] the goal of physical rehabilitation should be to restore and maintain each individual's highest attainable level of function and independence within the environment. Rehabilitation professionals should, without bias, creatively address clients' and or their caregivers expressed functional goals while incorporating the clinician's expertise in determining whether these expressed goals are realistic and the current levels of clinical evidence.[32]

THE PLAN OF CARE

Once an older adult's impairments and functional limitations have been identified, a rehabilitation plan of care is designed. The plan of care delineates specific goals, expected outcomes, specific interventions, intervention frequency, and the estimated duration of the plan of care. A plan of care should be considered a dynamic rather than a static process and is expected to evolve and change over the course of care.[12] It is important to reiterate that older adults frequently have multiple chronic diseases that affect multiple body systems, including the cardiovascular, pulmonary, neuromuscular, neurocognitive, integumentary, renal, and gastrointestinal systems.[13] Reevaluation of an individual's current health status and how it affects a patient's physical functioning and ability to participate in rehabilitation is a vital recursive process. Clinicians also use this information to identify specific precautions that need to be followed during treatment[14] and to determine whether specialty referral is indicated.[12]

Goal Setting

The development of specific goals for older adults with regional rheumatic disorders is based on the general goals presented in **Table 3**. The goals identified for each patient depend on the specific disorder, the severity of the disorder, the overall clinical presentation, and patient preferences.[13] Clinicians must remember that rehabilitation is active work done by the patient and not to the patient. Therefore, older adults' choices, desires, preferences, and expectations must be placed at the center of the process. Hence, the patient must be part of the goal-setting process. Psychological disorders and/or cognitive dysfunction may limit the collaborative process. Having thean opportunity to provide input on even the smallest aspects of the plan of care, however, can provide motivation for older adults.[35] It is the clinician's responsibility to ensure that the goals are realistic, objective, measurable, and time limited. In addition, goals and expected outcomes should be reviewed with the patient at regular intervals and modified as necessary.[12]

As discussed previously, setting realistic goals and measuring the outcomes or effectiveness or a rehabilitation intervention can be challenging. The Goal Attainment Scale (GAS) is a useful scale increasingly used by rehabilitation clinicians to select goals and measure outcomes from an intervention.[36] There are several advantages to using the GAS in rehabilitation:

- This scale allows the patient and the clinician to collaborate on setting a goal that is meaningful to the patient and is easily incorporated into clinical practice or as a research outcome measure.
- The GAS quantifies objectively the progress (or lack of progress) by objectively scoring the patient's response to treatment.
- The GAS is sensitive to change and less subject to floor and ceiling effects than many other measures.

Table 3
General goals and outcomes for individuals with regional rheumatic disorders

Impact of impairments in body structures/functions is reduced.	• Pain is decreased. • Range of motion of all joints is maximized and sufficient for functional activities. • Muscle activation and strength are maximized and sufficient for functional activities. • Joint stability is maximized and biomechanical stresses on all affected joints are decreased; deformity prevented. • Endurance is increased for all functional activities and desired recreational activities.
Ability to perform activities is improved.	• Independence in ADL is promoted, including dressing, transfers, and self-care. • Efficiency and safety of gait pattern and balance are improved. • Patterns of adequate physical activity or exercise to maintain or improve MSK and cardiovascular fitness and general health are established.
Health status and quality of life are improved.	Patient, family, and caregivers are educated to promote the individual's capacity for self-management.

Data from World Health Organization. Towards a common language for functioning, disability and health: ICF. Geneva (Switzerland): World Health Organization; 2002.

NONINVASIVE PROCEDURAL INTERVENTIONS

Rehabilitation professionals use information gathered through the history and examination to select interventions best suited to meet the individual's needs.[12] The selection of interventions may be affected not only by the impairments and goals but also by several psychosocial factors, including financial resources, social support, living environment, and the older adult's interests/motivation. To optimize this process, the intervention plan should be established and managed in collaboration with the older adult whenever possible. This collaboration is an important step toward empowering older adults to take responsibility for their own recovery.[35]

Noninvasive procedural interventions for older adults with regional rheumatic disorders focus on the following areas (**Table 4**):

- Pain relief (thermal agents, electrotherapy, and protective and supportive devices)
- Joint range of motion/flexibility
- Strengthening exercises
- Aerobic conditioning
- Functional training
- Aquatic exercise

PATIENT EDUCATION

Patient education is an essential component of health care. The patient (and/or caregiver) needs to take personal control over the prevention and management of the condition. Myths of the difficulties of older adults' ability to learn new material, however, often negatively influence the perception of health care providers. There exist age-related declines in attentiveness, concentration, performance, short-term memory, and speed of learning. Nevertheless, older adults, barring certain diseases, retain the ability to learn and understand well into late life. To compensate for age-related changes, a well-planned approach to instruction is necessary.[33] Rehabilitation professionals gain information about the older individual's learning style and learning capabilities and then adapt instructional sessions to enhance the learning process.

In summary, education on joint protection, energy conservation, and environmental adaptations is essential, because these are key components of self-management.

Joint Protection

Regional rheumatic disorders may render the involved joint weak and unstable; therefore, education on how to protect the joints is necessary. General joint protection principles include[13]

- Respect pain.
- Balance rest with activity.
- Exercise in a pain-free range.
- Avoid maintaining the joint in flexion for a prolonged period of time.
- Use large, strong joints.
- Use adaptive equipment/assistive devices as needed.

Energy Conservation

Energy conservation techniques are particularly useful for older adults who may have comorbidities resulting in impaired aerobic capacity. By conserving energy, older

Table 4
Procedural interventions for older adults with regional rheumatic disorders

Pain relief[a]	• Thermal agents ◦ Includes superficial heating modalities (eg, moist hot packs, paraffin wax, fluidotherapy), deep heating modalities (eg, US, diathermy), and cryotherapy (eg, cold packs, ice massage, cold therapy machines) ◦ Literature on the efficacy of thermal agents on pain in older adults is limited; however, they are frequently used clinically and in self-management of chronic pain among older adults.[17,35] ◦ Note contraindication/precautions for use ◦ Patient education on appropriate home use is essential because these modalities carry a risk of injury.[17] • TENS ◦ Literature on the efficacy of TENS is inconclusive, particularly for chronic pain.[17,35,36] Patients using TENS, however, have reported distraction from pain resulting in positive benefits, such as medication reduction, better function, psychological benefits, and better rest.[37] ◦ There is evidence that both conventional (high-frequency) and burst-mode TENS result in short-term pain relief in older adults with chronic pain. Patients reported conventional TENS, however, as more comfortable.[38] ◦ Note contraindication/precautions for use. ◦ Determining treatment parameters and educating patients/caregivers on appropriate use is essential, because this may influence effectiveness.[39] • Protective/supportive devices ◦ These devices may assist in decreasing pain and increasing function by supporting and protecting weak, fragile, or unbalanced muscles and joints.[35] ◦ Splinting may help preserve function by holding joints in a proper position and preventing tissue shortening or contracture.[40] ◦ Gait aids can assist with load transfer across joints.[17] ◦ Appropriate footwear and shoe orthotics may decrease loads across lower extremity joints and improve lower extremity alignment.[17] ◦ Decisions regarding use should be individualized based on information gained in the examination. Appropriate device selection and measurements are important in order to improve efficiency.[35] Cognition and coordination also influence the selection process.[33]
ROM/flexibility	• Static stretching is preferred to dynamic stretching for lengthening muscle and collagen tissue.[17] • Because of tissue extensibility changes in older adults, a 60-s hold is preferred to achieve long-term effects.[41] • Stretching exercises performed regularly, 5–7 d/wk, seem to be most effective.[41] • Stretching programs should be individualized based on the specific disorder and a patient's feedback regarding pain. • Stretching exercises in the presence of joint instability are contraindicated.[17]

(*continued on next page*)

Table 4 (*continued*)

Strengthening	• Well-designed strengthening programs improve function; decrease impact of chronic disease; and improve balance, coordination, speed of movement, and overall mobility. Strength training is often underused and undermanaged, however, for older adults.[17] • Strengthening programs should be progressive and individualized based on the specific disorder and a patient's feedback regarding pain. • High-intensity resistance training (80% of 1-repetition maximum) improves strength and function greater than low-intensity training and is safe when done properly.[42] • Eccentric training increases strength and function with less cardiovascular stress, especially in those who are deconditioned.[42] • Power training (plyometrics) can complement traditional training to improve speed and the ability to perform ADLs.[2,43] • Caution should be taken to ensure that older adults maintain proper form and avoid breath holding. It is recommended that high-intensity resistance training be done under the direct supervision of a physical therapist.[17]
Aerobic conditioning	• Involves continuous, rhythmic movement using large muscle groups • Increases the body's capacity to absorb, deliver, and use oxygen, thus improving the older adult's ability to complete desired activities without becoming fatigued[17] • Older adults' physical impairments, functional deficits, and personal goals need to be considered when selecting the mode of exercise. The mode should require little skill or extra equipment. • Be aware of any contraindication/precautions for aerobic exercise. Patients with undiagnosed or poorly managed cardiovascular symptoms should be referred for a medical evaluation before commencing aerobic conditioning. • Aquatic exercise ◦ A safe and beneficial alternative for older adults who cannot tolerate the stresses of land-based exercises because of pain or instability[17,42,44] ◦ Should be used in conjunction with land-based therapy for functional carryover[17,42,44] ◦ Individuals need to be able to move safely into and out of the pool and maneuver around the pool area.[17] ◦ May have an additional benefit of social support through group classes[42] ◦ Contraindicated for individuals with incontinence, open wounds, or allergies to the chemicals in pool water Other precautions/contraindications are the same as with any form of aerobic activity.[17]
Functional training	• Includes training in basic ADLs (eg, feeding, dressing, and self-care), functional mobility tasks (eg, bed mobility, transferring, and gait), and instrumental ADLs (eg, house chores and grocery shopping). Tasks targeted depend on the older adult's level of function. • Challenges individuals to use multiple joints through multiple axes of motion while incorporating body weight and balance • Has been shown to be more effective at improving functional task performance than resistance exercises alone[45] and flexibility exercises alone[46] • Should be performed in environments that are similar to those regularly encountered by the client[47,48] • Rehabilitation professionals may choose to use assistive devices/adaptive equipment to promote safety and maximize independence

Abbreviation: TENS, transcutaneous electrical nerve stimulation.

[a] These passive interventions should be used sparingly in conjunction with more active, functional interventions.[35]

Data from Refs.[17,33,35,37,39–46,49]

adults may be able to do more of the activities they enjoy with less pain and fatigue, in addition to completing their ADLs. These strategies include[32]

- Modifying activities (eg, sitting vs standing)
- Organizing activities to reduce redundancy of movement (eg, organizing household chores to reduce the number of times the stairs must be negotiated)
- Prioritizing tasks according to importance
- Delegating tasks to other individuals as appropriate

Environmental Adaptations

Normal age-related changes can affect older adults' ability to function safely in their home environments. The addition of a regional rheumatic disorder further complicates the situation. Adjustments to an older adult's existing environment can reduce the risk of falling, enhance independence, and improve quality of life.[50] Most environmental adaptations can be divided into 3 categories:

1. Removing hazards and improving efficiency (eg, removing clutter, cords, and throw rugs; placing frequently used items within reach).
2. Providing appropriate lighting (eg, using night lights and preventing excessive glare).
3. Installing adaptive equipment (eg, installing handrails on both sides of a staircase, grab bars in the bathroom, and tub bench/elevated toilet seat in the bathroom).

Rehabilitation professionals can provide guidance on which adaptations are needed and assist older adults (or caregivers) in prioritizing the needed changes.

INVASIVE PHYSIATRIC INTERVENTIONS

If a patient fails to improve with the noninvasive therapies described previously, enteral or topical medications and/or invasive interventions may be recommended.

Acupuncture/Dry Needling

Acupuncture and/or dry needling (ADN) are therapies commonly performed by physiatrists, physical therapists, and other practitioners. Pain is the most common diagnosis for which acupuncture is prescribed in a physiatric practice.[51] Reported benefits of ADN include analgesia, decreased swelling/edema, improved range of motion, and improved mood/affect. There is minimal risk with ADN and few contraindications other than infection at the site of pin insertion.[52]

Intra-articular Injections

Joint injections are performed either by palpation (using anatomic landmarks), with fluoroscopy, or increasingly with US guidance. Joint aspiration confirms intra-articular placement of the needle. Localization of some joints can be challenging and many physicians prefer image-based guidance for these procedures[53] (**Fig. 5**).

Intra-articular injections (IAIs) are commonly recommended for symptomatic relief. The most commonly recommended agents for IAI are corticosteroids or viscoagents (hyaluronic acid [HA]). Increasingly IAIs of so-called regenerative agents, including blood-derived products (platelet-rich plasma [PRP]) or prolotherapy, are offered to patients.[54]

Viscohyaluronic Acid

Several HA products are US Food and Drug Administration approved in the United States, and all are produced from in vitro bacterial fermentation or from harvested

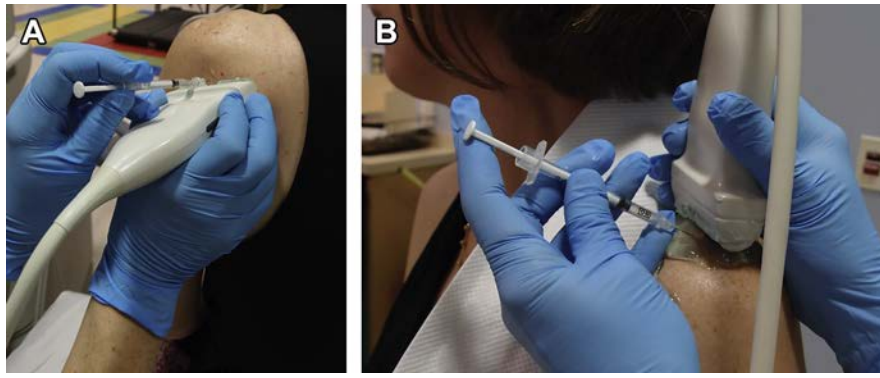

Fig. 5. (*A*) US-guided glenohumeral joint injection. (*B*) US-guided acromioclavicular joint injection.

combs of roosters. HA injection reportedly restores the viscoelastic properties of dysfunctional synovial fluids and may have a protective effect on hyaline cartilage and a disease-modifying effect for rheumatoid arthritis.[55] Given the heterogeneity of products, trial design, and patients, it is not surprising that studies report a range of benefits from HA injections.[56]

Regenerative Injections

Regenerative joint injections with PRP or prolotherapy are gaining acceptance by clinicians and patients and are an effective alternative to traditional agents. Although an increasing body of literature supports the efficacy of these agents,[54–61] they are generally considered complementary or alternative therapies and, therefore, not covered by third-party payers.

Prolotherapy

Prolotherapy refers to the injection of hypertonic dextrose solutions or, less commonly, morrhuate sodium into joints or other MSK structures, such as tendons and/or for other pain conditions.[52,57] The reported mechanism of action of prolotherapy is promotion of enhanced healing and tissue repair in a wide variety of MSK tissues, including tendons, muscle, ligaments, and joint cartilage with the formation of new collagen fibers.[58] Conditions for which prolotherapy may be recommended are wear and tear injuries of tendons, ligaments, and or cartilage, including tendinopathies, ligament strains, and cartilage defects.[54,57,58]

Platelet-Rich Plasma

PRP injections are reported to benefit patients with osteoarthritis, cartilage damage, epicondylosis, tendinosis, and other MSK conditions. PRP is an injectate derived from the platelet layer of autologous blood. Although there is a growing body of evidence that supports the safety and efficacy of PRP for the treatment of a wide variety of MSK conditions, additional high-quality placebo-controlled trials are needed.[59–61]

Soft Tissue Injections

Injection therapy is recommended for a wide variety of MSK soft tissue conditions, including myofascial pain conditions, trigger points, tendinopathies, epicondylosis,

Box 4
Future research topics to consider

- Optimizing the classification, nomenclature, and taxonomy of regional rheumatic disorders in older adults
- Completing a comprehensive epidemiologic study of regional rheumatic disorders in older adults
- Pursuing basic science research on soft tissues wear and tear
- Identifying clinical and diagnostic biomarkers for regional rheumatic disorders in older adults
- Studying the impact of comprehensive rehabilitation interventions in this population in relation to cost and function
- Systematic investigation of regenerative procedures and injections
- Studying the safety and efficacy of image-guided versus blind injection procedures

and muscle or ligament injuries. Injectate options include a wide variety of drugs/agents, including local anesthetics, corticosteroids, prolotherapy, PRP, botulinum toxins, and phenol ethers.[52,62] To select the most appropriate agent for each patients, clinicians must be familiar with the potential benefits and risks of each product. A full review of the other agents is beyond the scope of this article and readers are referred to reviews on this topic.[52,57,62]

Ultrasonography-Guided Needle Fenestration/Tenotomy

US-guided percutaneous needle fenestration or tenotomy is recommended as an alternative to surgery for refractory chronic tendinopathies.[63,64] The procedure involves repeatedly passing a needle through the area of degeneration, leading to local inflammation, bleeding, inflammation, and the release of growth factors. Commonly treated areas include the elbow, patella, Achilles tendon, and less commonly the hip or pubic symphysis. US-guided tenotomy combined with PRP injections has also been reported.[65] Studies show few complications and promising results.[63–65]

FUTURE RESEARCH CONSIDERATIONS

The number of older adults with and without regional rheumatic disorders will continue to grow over the next few decades. To optimize patients' functional independence for as long as feasible, it is important to gain an understanding of the disease process and its effects superimposed on the normal aging processes. Research topics to consider are listed in **Box 4**.

REFERENCES

1. Picavet HSJ, Hazes JMW. Prevalence of self reported musculoskeletal diseases is high. Ann Rheum Dis 2003;62:644–50.
2. Van Lankveld W, Goossens J, Franssen M. The gerontorheumatology outpatient service: toward the international classification of function-based health care provision for the elderly with musculoskeletal conditions: geriatric rheumatology: a comprehensive approach. Berlin: Springer Science + Business Media; 2011. p. 85–91.
3. Herr KA, Garand L. Assessment and measurement of pain in older adults. Pain Med 2007;8(7):585–601.

4. Borsheski R, Johnson QL. Pain management in the geriatric population. Mo Med 2014;111(6):508–11.
5. Auret K, Schug SA. Underutilisation of opioids in elderly patients with chronic pain. Drugs Aging 2005;22(8):641–54.
6. Ahmed MS, Matsumura B, Cristian A. Age-related changes in muscles and joints. Aging with a disability. Phys Med Rehabil Clin N Am 2005;16(1):16–39.
7. Tummala MK, Taubb DD, Ershler WB. Clinical immunology: immune senescence and the acquired immune deficiency of aging. In: Fillit HM, Rockwood K, Woodhouse K, editors. Brocklehurst's textbook of geriatric medicine and gerontology. 7th edition. Philadelphia: Saunders- Elsevier; 2010. p. 83–6.
8. de Lateur BJ. Rehabilitative strategies. In: Gonzalez-Fernandez M, Friedman JD, editors. Physical medicine and rehabilitation pocket companion. New York: Demos Medical. 2010; p. 1–3.
9. Lipsky P, Cush J. Approach to articular and musculoskeletal disorders. In: Fauci AS, editor. Harrison's rheumatology. New York (NY): McGraw-Hill; 2006. p. 227–39.
10. Speed C. Classification of soft tissue disorders: soft tissue rheumatology. Bethesda (Md): Oxford University Press; 2004. p. 141–5.
11. Biundo J Jr. Musculoskeletal signs and symptoms D. Regional rheumatic pain syndromes. In: Klippel JH, Stone JH, Croffor LJ, et al, editors. Primer on the rheumatic diseases. 13th edition. Springer; 2008. p. 68–86.
12. Guide to physical therapist practice 3.0. Alexandria (VA): American Physical Therapy Association; 2014. Available at: http://guidetoptpractice.apta.org. Accessed February 8, 2016.
13. O'Sullivan SB, Schmitz TJ, Fulk GD. Physical rehabilitation. Philadelphia: FA Davis; 2014.
14. Richards S, Cristian A. The role of the physical therapist in the care of the older adult. Clin Geriatr Med 2006;22(2):269–79.
15. Bloch RM. Geriatric rehabilitation. In: Braddom RL, Chan L, Harrast ML, et al, editors. Physical medicine and Rehabilitation. 4th edition. Elsevier; 2007. p. 1419–37.
16. Federal Interagency Forum on Aging-Related Statistics. Older Americans 2012: key indicators of well-being. Washington, DC: US Government Printing Office; 2012.
17. Vlieland TPV. Multidisciplinary team care and outcomes in rheumatoid arthritis. Curr Opin Rheumatol 2004;16(2):153–6.
18. Adler RS, Finzel KC. The complementary roles of MR imaging and ultrasound of tendons. Radiol Clin North Am 2005;43:771–807, ix.
19. Grassi W, Lamanna G, Farina A, et al. Sonographic imaging of normal and osteoarthritic cartilage. Semin Arthritis Rheum 1999;28:398–403.
20. Mathew AJ, Danda D, Conaghan PG. MRI and ultrasound in rheumatoid arthritis. Curr Opin Rheumatol 2016;28(3):323–9.
21. Smith J, Finnoff JT. Diagnostic and interventional musculoskeletal ultrasound: part 1. Fundamentals. PM R 2009;1(1):64–75.
22. Smith J, Finnoff JT. Diagnostic and interventional musculoskeletal ultrasound: part 2. Clinical applications. PM R 2009;1(2):162–77.
23. Finnoff JT. Musculoskeletal disorders of the upper limb. In: Braddom RL, Chan L, Harrast ML, et al, editors. Physical medicine and rehabilitation. 4th edition. Elsevier; 2007. p. 817–42.
24. Finnoff JT. Musculoskeletal disorders of the upper limb. In: Hazzard WR, Halter JB, editors. Hazzard's geriatric medicine and gerontology. New York: McGraw-Hill Medical; 2009. p. 162–77.

25. Hansen PA, Willick SE. Musculoskeletal disorders of the lower limb. In: Braddon RL, Chan L, Harrast ML, et al, editors. Physical medicine and rehabilitation. 4th edition. Elsevier; 2007. p. 843–70.
26. Frontera WR, Silver JK, Rizzo TD Jr. Essentials of physical medicine and rehabilitation, musculoskeletal disorders, pain and rehabilitation. 2nd edition. Saunders; 2008.
27. Griffin LY. Essentials of musculoskeletal care. 3rd edition. Washington, DC: AAOS; 2005.
28. Gilliland BC. Periarticular disorders of the extremities. In: Fauci AS, editor. Harrison's rheumatology. New York: McGraw Hill Medical; 2006. p. 299–302.
29. Beaton DE, Katz JN, Fossel AH, et al. Measuring the whole or the parts? Validity, reliability, and responsiveness of the Disabilities of the Arm, Shoulder and Hand outcome measure in different regions of the upper extremity. J Hand Ther 2001; 14(2):128–46.
30. Wade D. Rehabilitation - a new approach. Part two: the underlying theories. Clin Rehabil 2015;29(12):1145–54.
31. Stott D, Quinn T. Principles of rehabilitation of older people. Medicine 2013;41(1): 1–4.
32. Guccione A, Wong R, Avers D. Geriatric physical therapy. 3rd edition. St Louis (MO): Mosby; 2012.
33. Saxon SV, Etten MJ, Perkins EA. Physical change and aging: a guide for the helping professions. 6th edition. New York: Springer Publishing Company; 2014.
34. Centers for Medicare and Medicaid Services. Chronic conditions among Medicare beneficiaries, chartbook. 2012 edition. Baltimore (MD): Centers for Medicare and Medicaid Services; 2012.
35. Drench ME, Noonan A, Sharby N, et al. Psychosocial aspects of health care. 3rd edition. Upper Saddle River (NJ): Pearson Education; 2012.
36. Turner-Stokes L. Goal Attainment Scaling (GAS) in rehabilitation practice: a practical guide. Clin Rehabil 2009 Apr;23(4):362–70.
37. Abdulla A, Adams N, Bone M, et al. Guidance on the management of pain in older people. Age Ageing 2013;42(Suppl 1):i1–57.
38. Gladwell PW, Badlan K, Cramp F, et al. Direct and indirect benefits reported by users of transcutaneous electrical nerve stimulation for chronic musculoskeletal pain: qualitative exploration using patient interviews. Phys Ther 2015;95(11): 1518–28.
39. Barr J, Weissenbuehler S, Cleary C. Effectiveness and comfort of transcutaneous electrical nerve stimulation for older persons with chronic pain. J Geriatr Phys Ther 2004;27:93–9.
40. Bennett MI, Hughes N, Johnson MI. Methodological quality in randomized controlled trials of transcutaneous electric nerve stimulation for pain: low fidelity may explain negative findings. Pain 2011;152:1226–32.
41. Radomski MV, Trombly CA. Occupational therapy for physical dysfunction. Philadelphia: Wolters Kluwer Health; 2014.
42. Feland JB, Myrer JW, Schulthies SS, et al. The effect of duration of stretching of the hamstring muscle group for increasing range of motion in people aged 65 years and older. Phys Ther 2001;81:1110–7.
43. Kemmis K. The aging musculoskeletal system. Focus: physical therapist practice in geriatrics. Academy of Geriatric Physical Therapy 2011;1:1–31.
44. Cuoco A, Callahan DM, Sayers S, et al. Impact of muscle power and force on gait speed in disabled older men and women. J Gerontol A Biol Sci Med Sci 2004; 59(11):1200–6.

45. Takeshima N, Rogers ME, Watanabe E, et al. Water-based exercise improves health-related aspects of fitness in older women. Med Sci Sports Exerc 2002; 33:544–51.
46. de Vreede PL, Samson MM, van Meeteren NL, et al. Functional-task exercise versus resistance strength exercise to improve daily function in older women: a randomized, controlled trial. J Am Geriatr Soc 2005;53:2–10.
47. Alexander N, Galecki AT, Grenier ML, et al. Task-specific resistance training to improve the ability of activities of daily living-impaired older adults to rise from a bed and from a chair. J Am Geriatr Soc 2001;49(11):1418–27.
48. Jones CJ, Rose D. Physical activity instruction of older adults. Champaign (IL): Human Kinetics; 2005.
49. Edeer AO, Tuna H. Management of chronic musculoskeletal pain in the elderly: dilemmas and remedies. London (UK): INTECH Open Access Publisher; 2012.
50. Gillespie LD, Robertson MC, Gillespie WJ, et al. Interventions for preventing falls in older people living in the community. Cochrane Database Syst Rev 2012;(9):CD007146.
51. Tough EA, White AR, Cummings TM, et al. Acupuncture and dry needling in the management of myofascial trigger point pain: a systematic review and meta-analysis of randomized controlled trials. Eur J Pain 2009;13:3–10.
52. Singh V, Trescot A, Nishio I. Injections for chronic pain. Phys Med Rehabil Clin N Am 2015;26(2):249–61.
53. Davisdon J, Jayaraman S. Guided interventions in musculoskeletal ultrasound: what's the evidence? Clin Radiol 2011;66(2):140–52.
54. Rabago D, Zgierska A, Fortney L, et al. Hypertonic dextrose injections (prolotherapy) for knee osteoarthritis: results of a single-arm uncontrolled study with 1-year follow-up. J Altern Complement Med 2012;18(4):408–14.
55. Ayhan E, Kesmezacar H, Akgun S. Intraarticular injections (corticosteroid, hyaluronic acid, platelet rich plasma) for the knee osteoarthritis. World J Orthop 2014;5(3):351–61.
56. Bannuru RR, Natov NS, Dasi UR, et al. Therapeutic trajectory following intra-articular hyaluronic acid injection in knee osteoarthritis–meta-analysis. Osteoarthritis Cartilage 2011;19:611–9.
57. Fullerton BD, Reeves KD. Ultrasonography in regenerative injection (prolotherapy) using dextrose, platelet-rich plasma, and other injectants. Phys Med Rehabil Clin N Am 2010;21(3):585–605.
58. Park J, Song I, Lee J, et al. Ultrasonographic findings of healing of torn tendon in the patients with lateral epicondylitis after prolotherapy. J Korean Soc Med Ultrasonography 2003;22(3):177–83.
59. Palacio EP, Schiavetti RR, Kanematsu M, et al. Effects of platelet-rich plasma on lateral epicondylitis of the elbow: prospective randomized controlled trial. Rev Bras Ortop 2016;51(1):90–5.
60. Vannini F, Di Matteo B, Filardo G. Platelet-rich plasma to treat ankle cartilage pathology - from translational potential to clinical evidence: a systematic review. J Exp Orthop 2015;2(1):2.
61. Lai PL, Stitik TP, Foye PM, et al. Use of platelet-rich plasma in intra-articular knee injections for osteoarthritis: a systematic review. PM R 2015;7(6):637–48.
62. Alter K, Wilson N. Botulinum toxin therapy for musculoskeletal conditions. In: Alter KE, Wilson N, editors. Botulinum toxin injection manual. New York: Demos Medical Publishing; 2014. p. 260–84.

63. Jacobson JA, Rubin J, Yablon CM, et al. Ultrasound-guided fenestration of tendons about the hip and pelvis: clinical outcomes. J Ultrasound Med 2015; 34(11):2029–35.
64. Housner JA, Jacobson JA, Misko R. Sonographically guided percutaneous needle tenotomy for the treatment of chronic tendinosis. J Ultrasound Med 2009; 28(9):1187–92.
65. Finnoff JT, Fowler SP, Lai JK, et al. Treatment of chronic tendinopathy with ultrasound-guided needle tenotomy and platelet-rich plasma injection. PM R 2011;3(10):900–11.

Update on Cardiovascular Disease Risk in Patients with Rheumatic Diseases

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KEYWORDS

• Rheumatoid arthritis • Cardiovascular • Lipids • Lipoproteins • Myocardial fibrosis

KEY POINTS

- Cardiovascular disease (CVD) risk calculators underestimate CVD risk in rheumatoid arthritis (RA) and should be multiplied by 1.5 to reflect the greater than 1.5 times higher risk of CVD among adults with RA, even with no traditional CVD risk factors, although risk increases substantially with the number of CVD risk factors.
- Current CVD risk factors, particularly total and low-density lipoprotein (LDL)-C, likely underestimate the extent of subclinical atherosclerosis.
- LDL or high-density lipoprotein (HDL) particles, or apolipoprotein (apo)-B or ApoA1, may be more reliable CVD risk factors than cholesterol (total, LDL, or HDL) concentrations because of chronic inflammation.
- Reduction in inflammation may prevent or reduce myocardial injury and heart failure.
- Disease activity is a strong risk factor for CVD and mortality, and a key target for CVD risk reduction.

INTRODUCTION

Cardiovascular disease (CVD) risk is increased in rheumatoid arthritis (RA) and other inflammatory autoimmune rheumatic diseases, which have a lifetime risk of adult onset of 1 in 12 for women and 1 in 20 for men.[1] This review focuses on the most common RA, which occurs 2 to 3 times more often in women than men. The risk for CVD and total

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mortality is greater than 1.5 times higher in RA patients and 10-year CVD risk scores underestimate risk. CVD is more likely to be fatal, and unrecognized myocardial infarction (MI), sudden death, and heart failure (HF) are increased. More aggressive primary and secondary prevention of CVD is needed in RA patients,[2,3] many of whom are postmenopausal women. The current review focuses on the following (1) the role of dyslipidemia in RA-related CVD risk, (2) the risk of inflammation-related myocardial disease and eventual HF, and (3) the emergence of RA disease activity as a key focus for CVD risk prediction and CVD risk reduction in RA.

RA is associated with greater than 1.5-fold higher risk of coronary heart disease (CHD), CVD, HF,[4,5] venous thrombosis,[6,7] fatal CVD, total mortality,[8–10] and other CVD outcomes (**Box 1**). Unrecognized MI, sudden death,[11] and asymptomatic HF[12] are all increased among RA patients. The greater than 1.5-fold higher risk of CVD exists at most levels of traditional CVD risk factors, even among individuals with no smoking, diabetes, hypertension, or history of hypercholesterolemia, as shown in the Women's Health Initiative (WHI)-RA Study (crude relative risk is 10.75/6.35 = 1.69) (**Table 1**).[13] CVD risk in RA is strongly related to traditional CVD risk factors; for example, cigarette smoking, hypertension, diabetes, and hyperlipidemia.[13–16] The risk factor profile in RA (**Box 2**) includes higher prevalence of smoking, hypertension,[17] diabetes,[14] and obesity, although some RA patients have low body mass index (BMI).

In contrast, the role of dyslipidemia in RA has been questioned, due to a lipid paradox. RA patients have lower levels of total cholesterol (TC) and low-density lipoprotein (LDL) cholesterol (LDL-C) than adults without RA.[18] Increased CVD risk is associated with low levels of TC and LDL-C.[19] TC and LDL-C levels decrease before RA diagnosis,[20] often increase in response to antiinflammatory medications, and decrease in response to flares of RA disease activity. The paradoxically low TC and LDL-C levels in many RA patients contribute to underestimation of CVD risk by CVD risk scores (eg, Framingham Risk Score, Reynolds Risk Score,[21] and the Systematic Coronary Risk Evaluation [SCORE][22]). These have been shown to incorrectly classify as low risk approximately one-third of patients who subsequently had CVD events[22] and approximately 60% of RA patients with coronary artery calcification greater than 300.[23]

WHAT EXPLAINS THE EXCESS CARDIOVASCULAR DISEASE RISK IN RHEUMATOID ARTHRITIS?

Active RA is characterized by systemic inflammation that is credited with much of the excess risk of CVD and mortality in RA. The contribution of inflammation to

Box 1
Cardiovascular diseases increased in rheumatoid arthritis

- MI (often unrecognized)[11]
- Sudden death[11]
- Stroke[8]
- Venous thrombosis[6,7]
- HF[4,5]
- Diastolic dysfunction[63]
- Peripheral vascular disease[78]
- Subclinical atherosclerosis[52,54,55]
- Endothelial dysfunction[79]

Table 1
Weighted age-adjusted cardiovascular disease incidence rate (per 1000 person-years) among the Women's Health Initiative participants by risk factor combinations and groups of women with rheumatoid arthritis, with unverified rheumatoid arthritis, or not reporting rheumatoid arthritis[a]

	All Women with RA (Anti-CCP-Positive and/or Taking DMARDs)	Women with Unverified RA (Anti-CCP-Negative and Not Taking DMARDs)	Women with No Reported RA
No smoking, hypertension, diabetes mellitus, or high cholesterol			
Incidence (95% CI)	10.75 (5.75–20.89)[b,c]	8.28 (6.14–11.20)	6.35 (5.94–6.78)
Number of events per number of participants	25/217	125/1320	2480/36,299
Smoking only			
Incidence (95% CI)	16.99 (10.83–26.78)[b,c]	10.50 (8.09–13.65)	8.18 (7.72–8.66)
Number of events per number of participants	56/327	163/1445	3446/41,205
Hypertension only			
Incidence (95% CI)	16.99 (8.13–37.74)	15.36 (11.77–20.20)	12.53 (11.72–13.41)
Number of events per number of participants	19/106	161/907	2540/17,297
Hypertension and smoking only			
Incidence (95% CI)	27.35 (16.80–45.21)[b,c]	18.50 (14.39–23.84)	16.59 (15.63–17.61)
Number of events per number of participants	45/179	186/941	3253/18,041
Diabetes mellitus and hypertension only			
Incidence (95% CI)	45.72 (10.98–216.51)	37.77 (22.09–65.29)	27.03 (23.14–31.60)
Number of events per number of participants	5/16	43/124	477/1746

[a] Excluding those with CVD at baseline or RA only at follow-up.
[b] $P<.05$ versus women with unverified RA.
[c] $P<.05$ versus women with no reported RA.
From Mackey RH, Kuller LH, Deane KD, et al. Rheumatoid arthritis, anti-cyclic citrullinated peptide positivity, and cardiovascular disease risk in the Women's Health Initiative. Arthritis Rheumatol 2015;67(9):2315; with permission.

atherosclerosis, endothelial dysfunction, plaque vulnerability, and atherothrombotic events has been previously reviewed.[24] In RA, CVD risk reduction has been reported using several antiinflammatory disease-modifying antirheumatic drugs (DMARDs), including hydroxychloroquine[25] and methotrexate,[26] and possibly for tumor necrosis factor (TNF)-α inhibitors.[27] Recently, The Canakinumab Antiinflammatory Thrombosis Outcome Study (CANTOS) trial reported that among adults with prior MI but not RA, antiinterleukin (IL)-1β antibody (canakinumab) reduced CVD events (nonfatal MI and stroke and CVD death).[28] RA-associated inflammation also contributes to the development of dysfunctional high-density lipoprotein (HDL).[29] However, as noted, primary and secondary prevention of CVD may have been suboptimal in RA subjects,[2,3] most of whom are postmenopausal women without elevated LDL-C.

This review focuses on the following issues: (1) reconsideration of the role of dyslipidemia in CVD risk, (2) potential role of inflammation on myocardial disease and eventual HF, and (3) the emerging role of disease activity as key for CVD risk prediction and CVD risk reduction in RA.

Box 2
Cardiovascular disease risk factors in rheumatoid arthritis patients

- ↑ Smoking, past, current
- ↑ Hypertension
- ↑ Diabetes
- ↓ TC and LDL-cholesterol (sometimes with ↓ HDL-cholesterol and ↑ triglycerides)
- ↓ Physical activity
- ↑ Obesity and ↓ low BMI
- ↑ Inflammation (CRP, ESR, cytokines)
- ↑ Dysfunctional HDL
- ↑ ApoB, LDL-P
- ↑ Lipoprotein(a)

↑, increase; ↓, decrease.

ROLE OF DYSLIPIDEMIA IN CARDIOVASCULAR DISEASE RISK IN RHEUMATOID ARTHRITIS

Can Lipoprotein Particle Concentrations Explain the Lipid Paradox in Rheumatoid Arthritis?

The lipid paradox in RA describes the seemingly paradoxic association of low levels of TC and LDL-C with increased CVD risk.[19] However, recent large studies show a J-shaped association of LDL-C with CVD in RA[30,31] that is similar to non-RA controls.[31] Indeed, the lipid paradox of high CVD risk with normal or low LDL-C is well known in adults with the metabolic syndrome, diabetes, or obesity. These conditions are characterized by increased levels of inflammation; triglycerides; and small, dense, cholesterol-depleted LDL particles (LDL-P) despite decreased levels of LDL-C. LDL-P can be measured directly or estimated by ApoB, which quantifies atherogenic lipoprotein particles LDL and VLDL (very low density lipoprotein), of which greater than or equal to 90% of are LDL-P. When discordance exists between concentrations of atherogenic lipoproteins (eg, ApoB, LDL-P) and their cholesterol content (LDL-C or non-HDL-C), CVD risk is better estimated using particle concentrations rather than cholesterol level, as demonstrated in the Multi-Ethnic Study of Atherosclerosis (**Fig. 1**)[32] and other studies.[33–35] The effect of HDL on CVD risk is much more complicated, but CVD risk and HDL functionality appear to be more strongly related to concentrations of HDL particles (HDL-P) and ApoA1 than to HDL cholesterol.[36]

Similarly, lipoprotein particle or apolipoprotein (apo) concentrations (ApoB, LDL-P, ApoA1, and HDL-P) may be useful in CVD risk assessment in RA. In many studies, ApoB or the ApoB to ApoA1 ratio are associated with progression of atherosclerosis in the carotid[37] and coronary arteries,[38] and are independently associated with CVD risk when TC and LDL-C are not.[39,40] Recent studies also suggest that LDL-P greater than LDL-C or ApoB greater than LDL-C discordance is common in RA. Several studies report that, compared with controls, RA subjects have higher levels of small LDL-P[41,42] and higher levels of ApoB (and triglycerides) despite similar LDL-C levels,[38,43] similar levels of LDL-P, or lower levels of LDL-C[44] (ie, ApoB > LDL-C or LDLP > LDL-C discordance). Measuring lipoprotein particles or apolipoproteins provides more reliable information regarding risk and effects of disease activity and medications. Equivalent population cutpoints for LDL-C, non-HDL-C, LDL-P, and

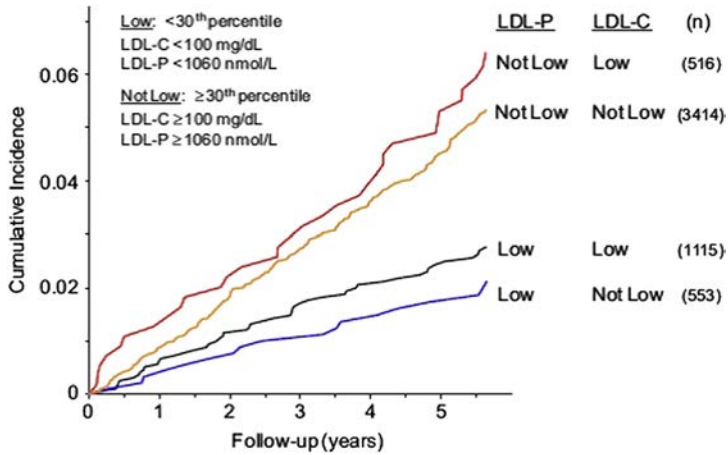

Fig. 1. Cumulative incidence of cardiovascular events in subgroups with low LDL-C and/or low LDL-P, from proportional hazards models adjusted for age and gender. Low LDL-C and LDL-P values were defined as less than 100 mg/dL and less than 1060 nmol/L, respectively (<30th percentile). (*From* Otvos JD, Mora S, Shalaurova I, et al. Clinical implications of discordance between low-density lipoprotein cholesterol and particle number. J Clin Lipidol 2011;5(2):110; with permission.)

ApoB have been described.[45] More importantly, these results emphasize the role of dyslipidemia in RA. For this reason, statin therapy, which reduces LDL-P, ApoB, and LDL-C levels,[46] and reduces CVD events in adults with low LDL-C but elevated C-reactive protein (CRP),[47] is very important adjunct therapy in RA patients.

Recent recommendations for dyslipidemia management from the National Lipid Association (NLA) specifically address RA.[48] NLA recommendations include counting RA is as an additional atherosclerotic CVD risk factor for risk stratification, rechecking LDL-C levels after RA flare, and using non-HDL-C, ApoB, or LDL-P concentration instead of LDL-C when discordance exists.[48] These recommendations are similar to the European League Against Rheumatism's recently updated recommendations for CVD risk management in individuals with RA and other inflammatory joint diseases.[49] Updated recommendations include optimal control of disease activity. CVD risk assessment should be done at least every 5 years using national guidelines; however, CVD risk scores should be multiplied by 1.5 for all RA patients (and possibly for ankylosing spondylitis and psoriatic arthritis.) TC and HDL-C should be used for risk assessment but ideally should be measured when disease activity is stable or in remission. Ultrasound screening for asymptomatic carotid plaques may be considered as part of risk evaluation. Finally, antihypertensive medications and statins may be used as in the general population.[49]

Current Risk Factors in Rheumatoid Arthritis Patients Underestimate Prior Exposures and Burden of Atherosclerosis

Among RA patients, current levels of smoking, lipids, BMI, and other risk factors underestimate CVD risk. A substantial portion of this unexplained excess risk seems related to an accelerated burden of subclinical atherosclerosis that develops before the clinical features of RA. CVD risk is substantially increased at RA diagnosis,[16] and even before RA diagnosis, with a 3-fold higher chance of MI in the 2 years before diagnosis.[11] Studies suggest that lipids may be elevated, then decrease, before RA diagnosis. Ten years before the diagnosis of RA, individuals who develop RA have

higher levels of ApoB (+6%), TC (+4%), triglycerides (+17%), and lower HDL-C (−9%) than individuals who did not develop RA.[50] Another study showed that in the 5 years before RA diagnosis, levels of TC and LDL-C decreased but levels of triglycerides, which are a strong predictor of higher ApoB and LDL-P levels, did not.[20]

Substantially Increased Burden of Atherosclerosis at Diagnosis of Rheumatoid Arthritis?

Increased subclinical atherosclerosis compared with controls is seen in early RA,[51,52] with a similar prevalence of carotid plaques but faster progression of carotid intima-media thickness (cIMT) in early RA versus late RA.[53] Among individuals with RA, the extent of calcified plaque in the aorta and coronary and carotid arteries may be more than 10 years ahead of non-RA controls (**Fig. 2**).[54] Among RA patients, even among those aged less than 40 years, 50% of RA patients had calcified plaque in a least 1 of the 3 vascular sites. The presence of calcified plaque increased to 75% for those ages 50 to 60 years, and greater than 90% for those aged greater than 60 years.[54] Other studies show that, in RA, noncalcified coronary plaque, which is not detected by these measures but may be more vulnerable, is more common than calcified plaque.[55] Importantly, carotid plaque and cIMT have been shown to predict CVD events in RA.[56]

Inflammation May Cause Myocardial Disease Directly, Leading to Heart Failure

The risk of HF in RA is increased more than 2-fold and is poorly explained by CVD risk factors or ischemic heart disease.[57] One study showed increased myocardial ischemia in RA subjects who had no evidence of obstructive coronary artery disease.[58] Inflammatory markers that are increased in RA (eg, erythrocyte sedimentation rate [ESR], CRP, white blood cell count, and cytokines, including IL-6 and TNF-α) have stronger associations with fatal CVD, mortality, and HF than with atherosclerosis and MI.[59–61] Evidence suggests that inflammation contributes to myocardial microvascular endothelial dysfunction, remodeling, interstitial fibrosis, and diastolic dysfunction, leading to HF, specifically with preserved ejection

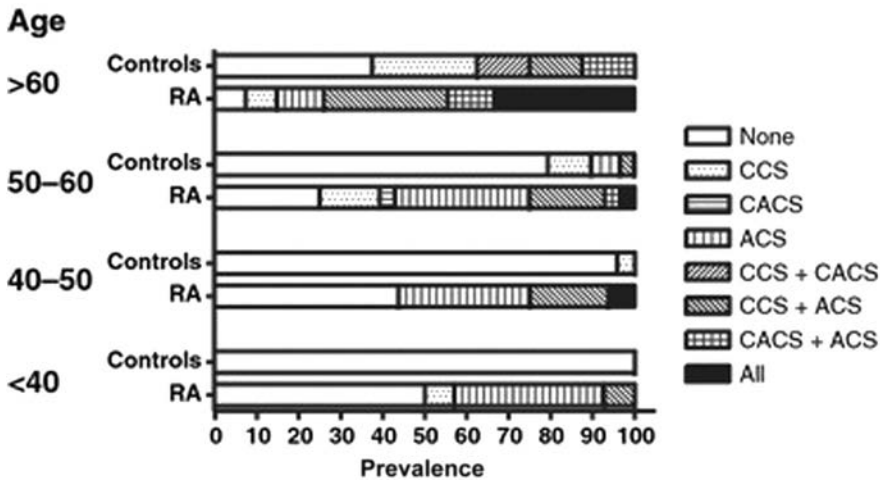

Fig. 2. Prevalence and distribution of vascular calcification in coronary (CACS), aortic (ACS), and carotid arteries (CCS) by age in control subjects and patients with RA. (*From* Wang S, Yiu KH, Mok MY, et al. Prevalence and extent of calcification over aorta, coronary and carotid arteries in patients with rheumatoid arthritis. J Intern Med 2009;266(5):449; with permission.)

fraction.[62] HF in RA is more often HF with preserved ejection fraction, and fatal,[12] and RA is associated with diastolic dysfunction,[63] left ventricular remodeling,[64] and reduced left ventricular mass.[65] RA patients have elevated levels of MRI-measured myocardial fibrosis, which is associated with myocardial dysfunction and higher RA disease activity.[66,67] Two recent studies have reported improvements in cardiac MRI-detected function following 1 year of treatment with DMARDs[68] or tocilizumab.[69] Future assessments of antiinflammatory medications and other RA interventions will likely include measures of subclinical myocardial fibrosis and damage.

Emergence of Rheumatoid Arthritis Disease Activity as Key Predictor and Target for Prevention of Cardiovascular Disease Risk

RA treatment seeks to reduce disease activity. It is assessed using various scores based on numbers of swollen and tender joints, with or without inflammatory markers, such as ESR or CRP. Increasing evidence indicates that reducing RA disease activity is critical for CVD risk prevention. Recent studies showed strong associations of disease activity (cumulative, flares or joint pain) with increased CVD risk.[39,70] Importantly, with anti-IL-6 treatment, greater reductions in disease activity and swollen and tender joint counts were independently related to lower CVD risk during follow-up.[39] Furthermore, as noted, higher disease activity is associated with MRI-detected myocardial fibrosis.[60,71]

Inflammation may explain (i.e., contribute to) the association of higher disease activity with higher cIMT,[72] incidence of carotid plaque, progression of carotid plaque over 3 years[53] and vulnerability of coronary[55] and carotid plaque.[73] Disease activity may also increase CVD risk indirectly via effects of joint symptoms on physical activity and adherence to certain types of risk factor modification.[74] Interrelationships of disease activity, inflammation, and joint pain may explain WHI-RA study results showing that joint pain severity was associated with higher CHD incidence among postmenopausal women with RA but also among women with unspecified arthritis, and among women without RA or arthritis.[13] Even among women with RA, absence of joint pain was associated with low CVD risk,[13] supporting the importance of tight control of disease activity to reduce CVD risk.

A new RA-specific CVD risk calculator, the Extended Risk Score–Rheumatoid Arthritis, found that risk prediction from traditional CVD risk factors was improved by the following: clinical disease activity index (which does not include CRP or other inflammation markers), disability (Health Assessment Questionnaire), disease duration greater than 10 years, and prednisone use.[75] In contrast, seropositivity (i.e., positivity for Rheumatoid Factor [RF]+, or antibodies to cyclic citrullinated peptides [anti-CCP+ or ACPA+]), erosions, and subcutaneous nodules were not significantly associated with CVD risk. Because RA-specific CVD risk factors (**Box 3**) are associated with increased RA disease severity, tight control of disease activity may reduce their association with higher CVD risk.

It is also possible that anti-CCP+ and RF+ may be directly related to HF and total mortality through effects on lungs or kidneys. For example, over a 36-year follow-up in the Nurses' Health Study, respiratory mortality was increased among women with seropositive RA (hazard ratio 2.67, 95% CI 1.89–3.77) but not with seronegative RA compared with women without RA.[76] Those results agree with a report of greater immune cell accumulation and activation in lung tissue of anti-CCP+ RA versus anti-CCP-negative RA and controls.[77] However, as noted, current recommendations multiply CVD risk scores by 1.5[49] or use RA as an additional risk factor,[48] regardless of seropositivity or other RA severity indices.

Box 3
Rheumatoid arthritis: specific cardiovascular disease risk factors

- Disease activity (scores of joint pain, inflammation)
- Disease duration (>10 years)
- Seropositivity (anti-CCP+ or RF+)
- Rheumatoid nodules
- Extraarticular disease
- Inflammatory markers
- HLA shared epitope

SUMMARY

The risk of CVD and death is increased greater than or equal to 1.5-fold among adults with RA, most of whom are postmenopausal women. CVD risk scores underestimate their CVD risk due to an accelerated burden of subclinical atherosclerosis before diagnosis and changes in postdiagnosis risk factor levels (decreased lipids, possibly smoking). Current recommendations include multiplying risk scores by 1.5, considering subclinical disease burden, and use of statins and antihypertensive medications. Aggressive management and control of risk factors, including smoking cessation and antihypertensive and lipid-lowering medications, is needed at earlier ages. Reducing disease activity and inflammation may be essential for reducing myocardial disease and fibrosis of the heart, lung, and kidney. Further evaluation with new imaging techniques are needed to determine effects of antiinflammatory drugs on myocardial, lung, and kidney fibrosis. Clinical trials of antiinflammatory medications will provide additional evidence to target inflammation reduction to reduce the risk of CHD, CVD, and total mortality.

REFERENCES

1. Crowson CS, Matteson EL, Myasoedova E, et al. The lifetime risk of adult-onset rheumatoid arthritis and other inflammatory autoimmune rheumatic diseases. Arthritis Rheum 2011;63(3):633–9.
2. Bartels CM, Kind AJ, Thorpe CT, et al. Lipid testing in patients with rheumatoid arthritis and key cardiovascular-related comorbidities: a Medicare analysis. Semin Arthritis Rheum 2012;42(1):9–16.
3. Bartels CM, Saucier JM, Thorpe CT, et al. Monitoring diabetes in patients with and without rheumatoid arthritis: a Medicare study. Arthritis Res Ther 2012;14(4):R166.
4. Nicola PJ, Crowson CS, Maradit-Kremers H, et al. Contribution of congestive heart failure and ischemic heart disease to excess mortality in rheumatoid arthritis. Arthritis Rheum 2006;54(1):60–7.
5. Nicola PJ, Maradit-Kremers H, Roger VL, et al. The risk of congestive heart failure in rheumatoid arthritis: a population-based study over 46 years. Arthritis Rheum 2005;52(2):412–20.
6. Holmqvist ME, Neovius M, Eriksson J, et al. Risk of venous thromboembolism in patients with rheumatoid arthritis and association with disease duration and hospitalization. JAMA 2012;308(13):1350–6.
7. Bacani AK, Gabriel SE, Crowson CS, et al. Noncardiac vascular disease in rheumatoid arthritis: increase in venous thromboembolic events? Arthritis Rheum 2012;64(1):53–61.

8. Meune C, Touze E, Trinquart L, et al. High risk of clinical cardiovascular events in rheumatoid arthritis: levels of associations of myocardial infarction and stroke through a systematic review and meta-analysis. Arch Cardiovasc Dis 2010; 103(4):253–61.
9. Meune C, Touze E, Trinquart L, et al. Trends in cardiovascular mortality in patients with rheumatoid arthritis over 50 years: a systematic review and meta-analysis of cohort studies. Rheumatology 2009;48(10):1309–13.
10. Avina-Zubieta JA, Choi HK, Sadatsafavi M, et al. Risk of cardiovascular mortality in patients with rheumatoid arthritis: a meta-analysis of observational studies. Arthritis Rheum 2008;59(12):1690–7.
11. Maradit-Kremers H, Crowson CS, Nicola PJ, et al. Increased unrecognized coronary heart disease and sudden deaths in rheumatoid arthritis: a population-based cohort study. Arthritis Rheum 2005;52(2):402–11.
12. Davis JM 3rd, Roger VL, Crowson CS, et al. The presentation and outcome of heart failure in patients with rheumatoid arthritis differs from that in the general population. Arthritis Rheum 2008;58(9):2603–11.
13. Mackey RH, Kuller LH, Deane KD, et al. Rheumatoid arthritis, anti-cyclic citrullinated peptide positivity, and cardiovascular disease risk in the Women's Health Initiative. Arthritis Rheumatol 2015;67(9):2311–22.
14. Boyer JF, Gourraud PA, Cantagrel A, et al. Traditional cardiovascular risk factors in rheumatoid arthritis: a meta-analysis. Jointt Bone Spine 2011;78(2):179–83.
15. Solomon DH, Curhan GC, Rimm EB, et al. Cardiovascular risk factors in women with and without rheumatoid arthritis. Arthritis Rheum 2004;50(11):3444–9.
16. Kremers HM, Crowson CS, Therneau TM, et al. High ten-year risk of cardiovascular disease in newly diagnosed rheumatoid arthritis patients: a population-based cohort study. Arthritis Rheum 2008;58(8):2268–74.
17. Chung CP, Giles JT, Petri M, et al. Prevalence of traditional modifiable cardiovascular risk factors in patients with rheumatoid arthritis: comparison with control subjects from the multi-ethnic study of atherosclerosis. Semin Arthritis Rheum 2012;41(4):535–44.
18. Liao KP, Cai T, Gainer VS, et al. Lipid and lipoprotein levels and trend in rheumatoid arthritis compared to the general population. Arthritis Care Res 2013;65(12): 2046–50.
19. Myasoedova E, Crowson CS, Kremers HM, et al. Lipid paradox in rheumatoid arthritis: the impact of serum lipid measures and systemic inflammation on the risk of cardiovascular disease. Ann Rheum Dis 2011;70(3):482–7.
20. Myasoedova E, Crowson CS, Kremers HM, et al. Total cholesterol and LDL levels decrease before rheumatoid arthritis. Ann Rheum Dis 2010;69(7):1310–4.
21. Crowson CS, Matteson EL, Roger VL, et al. Usefulness of risk scores to estimate the risk of cardiovascular disease in patients with rheumatoid arthritis. Am J Cardiol 2012;110(3):420–4.
22. Arts EE, Popa C, Den Broeder AA, et al. Performance of four current risk algorithms in predicting cardiovascular events in patients with early rheumatoid arthritis. Ann Rheum Dis 2015;74(4):668–74.
23. Kawai VK, Chung CP, Solus JF, et al. The ability of the 2013 American College of Cardiology/American Heart Association cardiovascular risk score to identify rheumatoid arthritis patients with high coronary artery calcification scores. Arthritis Rheumatol 2015;67(2):381–5.
24. Ridker PM. From C-reactive protein to interleukin-6 to interleukin-1: moving upstream to identify novel targets for atheroprotection. Circ Res 2016; 118(1):145–56.

25. Sharma TS, Wasko MC, Tang X, et al. Hydroxychloroquine use is associated with decreased incident cardiovascular events in rheumatoid arthritis patients. J Am Heart Assoc 2016;5(1) [pii:e002867].
26. Micha R, Imamura F, Wyler von Ballmoos M, et al. Systematic review and meta-analysis of methotrexate use and risk of cardiovascular disease. Am J Cardiol 2011;108(9):1362–70.
27. Barnabe C, Martin BJ, Ghali WA. Systematic review and meta-analysis: anti-tumor necrosis factor alpha therapy and cardiovascular events in rheumatoid arthritis. Arthritis Care Res 2011;63(4):522–9.
28. Ridker PM, Everett BM, Thuren T, et al. Antiinflammatory therapy with canakinumab for atherosclerotic disease. N Engl J Med 2017;377(12):1119–31.
29. Ormseth MJ, Stein CM. High-density lipoprotein function in rheumatoid arthritis. Curr Opin Lipidol 2016;27(1):67–75.
30. Zhang J, Chen L, Delzell E, et al. The association between inflammatory markers, serum lipids and the risk of cardiovascular events in patients with rheumatoid arthritis. Ann Rheum Dis 2014;73(7):1301–8.
31. Liao KP, Liu J, Lu B, et al. Association between lipid levels and major adverse cardiovascular events in rheumatoid arthritis compared to non-rheumatoid arthritis patients. Arthritis Rheumatol 2015;67(8):2004–10.
32. Otvos JD, Mora S, Shalaurova I, et al. Clinical implications of discordance between low-density lipoprotein cholesterol and particle number. J Clin Lipidol 2011;5(2):105–13.
33. Sniderman AD, Islam S, Yusuf S, et al. Discordance analysis of apolipoprotein B and non-high density lipoprotein cholesterol as markers of cardiovascular risk in the INTERHEART study. Atherosclerosis 2012;225(2):444–9.
34. Pencina MJ, D'Agostino RB, Zdrojewski T, et al. Apolipoprotein B improves risk assessment of future coronary heart disease in the Framingham Heart Study beyond LDL-C and non-HDL-C. Eur J Prev Cardiol 2015;22(10):1321–7.
35. Lawler PR, Akinkuolie AO, Ridker PM, et al. Discordance between circulating atherogenic cholesterol mass and lipoprotein particle concentration in relation to future coronary events in women. Clin Chem 2017;63(4):870–9.
36. Mackey RH, Greenland P, Goff DC Jr, et al. High-density lipoprotein cholesterol and particle concentrations, carotid atherosclerosis, and coronary events: MESA (multi-ethnic study of atherosclerosis). J Am Coll Cardiol 2012;60(6):508–16.
37. Ajeganova S, Ehrnfelt C, Alizadeh R, et al. Longitudinal levels of apolipoproteins and antibodies against phosphorylcholine are independently associated with carotid artery atherosclerosis 5 years after rheumatoid arthritis onset–a prospective cohort study. Rheumatology 2011;50(10):1785–93.
38. Knowlton N, Wages JA, Centola MB, et al. Apolipoprotein B-containing lipoprotein subclasses as risk factors for cardiovascular disease in patients with rheumatoid arthritis. Arthritis Care Res 2012;64(7):993–1000.
39. Rao VU, Pavlov A, Klearman M, et al. An evaluation of risk factors for major adverse cardiovascular events during tocilizumab therapy. Arthritis Rheumatol 2015;67(2):372–80.
40. Ohman M, Ohman ML, Wallberg-Jonsson S. The ApoB/ApoA1 ratio predicts future cardiovascular events in patients with rheumatoid arthritis. Scand J Rheumatol 2014;43(4):259–64.
41. Hurt-Camejo E, Paredes S, Masana L, et al. Elevated levels of small, low-density lipoprotein with high affinity for arterial matrix components in patients with rheumatoid arthritis: possible contribution of phospholipase A2 to this atherogenic profile. Arthritis Rheum 2001;44(12):2761–7.

42. Rizzo M, Spinas GA, Cesur M, et al. Atherogenic lipoprotein phenotype and LDL size and subclasses in drug-naive patients with early rheumatoid arthritis. Atherosclerosis 2009;207(2):502–6.
43. Choi HK, Seeger JD. Lipid profiles among US elderly with untreated rheumatoid arthritis–the Third National Health and Nutrition Examination Survey. J Rheumatol 2005;32(12):2311–6.
44. Charles-Schoeman C, Fleischmann R, Davignon J, et al. Potential mechanisms leading to the abnormal lipid profile in patients with rheumatoid arthritis versus healthy volunteers and reversal by tofacitinib. Arthritis Rheumatol 2015;67(3):616–25.
45. Contois JH, McConnell JP, Sethi AA, et al. Apolipoprotein B and cardiovascular disease risk: position statement from the AACC lipoproteins and vascular diseases division working group on best practices. Clin Chem 2009;55(3):407–19.
46. Rosenson RS, Otvos JD, Hsia J. Effects of rosuvastatin and atorvastatin on LDL and HDL particle concentrations in patients with metabolic syndrome: a randomized, double-blind, controlled study. Diabetes care 2009;32(6):1087–91.
47. Ridker PM, Danielson E, Fonseca FA, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med 2008;359(21):2195–207.
48. Jacobson TA, Maki KC, Orringer CE, et al. National Lipid Association recommendations for patient-centered management of dyslipidemia: part 2. J Clin Lipidol 2015;9(6 Suppl):S1–122.
49. Agca R, Heslinga SC, Rollefstad S, et al. EULAR recommendations for cardiovascular disease risk management in patients with rheumatoid arthritis and other forms of inflammatory joint disorders: 2015/2016 update. Ann Rheum Dis 2017;76(1):17–28.
50. van Halm VP, Nielen MM, Nurmohamed MT, et al. Lipids and inflammation: serial measurements of the lipid profile of blood donors who later developed rheumatoid arthritis. Ann Rheum Dis 2007;66(2):184–8.
51. Hannawi S, Haluska B, Marwick TH, et al. Atherosclerotic disease is increased in recent-onset rheumatoid arthritis: a critical role for inflammation. Arthritis Res Ther 2007;9(6):R116.
52. Ambrosino P, Lupoli R, Di Minno A, et al. Subclinical atherosclerosis in patients with rheumatoid arthritis. A meta-analysis of literature studies. Thromb Haemost 2015;113(5):916–30.
53. Giles JT, Post WS, Blumenthal RS, et al. Longitudinal predictors of progression of carotid atherosclerosis in rheumatoid arthritis. Arthritis Rheum 2011;63(11):3216–25.
54. Wang S, Yiu KH, Mok MY, et al. Prevalence and extent of calcification over aorta, coronary and carotid arteries in patients with rheumatoid arthritis. J Intern Med 2009;266(5):445–52.
55. Karpouzas GA, Malpeso J, Choi TY, et al. Prevalence, extent and composition of coronary plaque in patients with rheumatoid arthritis without symptoms or prior diagnosis of coronary artery disease. Ann Rheum Dis 2014;73(10):1797–804.
56. Ikdahl E, Rollefstad S, Wibetoe G, et al. Predictive value of arterial stiffness and subclinical carotid atherosclerosis for cardiovascular disease in patients with rheumatoid arthritis. J Rheumatol 2016;43(9):1622–30.
57. Crowson CS, Nicola PJ, Kremers HM, et al. How much of the increased incidence of heart failure in rheumatoid arthritis is attributable to traditional

cardiovascular risk factors and ischemic heart disease? Arthritis Rheum 2005;52(10):3039–44.
58. Toutouzas K, Sfikakis PP, Karanasos A, et al. Myocardial ischaemia without obstructive coronary artery disease in rheumatoid arthritis: hypothesis generating insights from a cross-sectional study. Rheumatology (Oxford) 2013;52:76–80.
59. Ajeganova S, Andersson ML, Frostegard J, et al. Disease factors in early rheumatoid arthritis are associated with differential risks for cardiovascular events and mortality depending on age at onset: a 10-year observational cohort study. J Rheumatol 2013;40:1958–66.
60. Maradit-Kremers H, Nicola PJ, Crowson CS, et al. Cardiovascular death in rheumatoid arthritis: a population-based study. Arthritis Rheum 2005;52:722–32.
61. Maradit-Kremers H, Nicola PJ, Crowson CS, et al. Raised erythrocyte sedimentation rate signals heart failure in patients with rheumatoid arthritis. Ann Rheum Dis 2007;66:76–80.
62. Paulus WJ, Tschope C. A novel paradigm for heart failure with preserved ejection fraction: comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. J Am Coll Cardiol 2013;62(4): 263–71.
63. Aslam F, Bandeali SJ, Khan NA, et al. Diastolic dysfunction in rheumatoid arthritis: a meta-analysis and systematic review. Arthritis Care Res 2013; 65(4):534–43.
64. Myasoedova E, Davis JM 3rd, Crowson CS, et al. Brief report: rheumatoid arthritis is associated with left ventricular concentric remodeling: results of a population-based cross-sectional study. Arthritis Rheum 2013;65(7):1713–8.
65. Giles JT, Malayeri AA, Fernandes V, et al. Left ventricular structure and function in patients with rheumatoid arthritis, as assessed by cardiac magnetic resonance imaging. Arthritis Rheum 2010;62(4):940–51.
66. Ntusi NA, Piechnik SK, Francis JM, et al. Diffuse myocardial fibrosis and inflammation in rheumatoid arthritis: insights from CMR T1 mapping. JACC Cardiovasc Imaging 2015;8(5):526–36.
67. Kobayashi Y, Giles JT, Hirano M, et al. Assessment of myocardial abnormalities in rheumatoid arthritis using a comprehensive cardiac magnetic resonance approach: a pilot study. Arthritis Res Ther 2010;12(5):R171.
68. Lehmonen L, Vuorinen AM, Koivuniemi R, et al. One-year follow-up study detects myocardial changes with cardiovascular magnetic resonance tagging in active rheumatoid arthritis. Acad Radiol 2018;25(4):476–85.
69. Kobayashi Y, Kobayashi H, Giles JT, et al. Association of tocilizumab treatment with changes in measures of regional left ventricular function in rheumatoid arthritis, as assessed by cardiac magnetic resonance imaging. Int J Rheum Dis 2016;19(11):1169–74.
70. Myasoedova E, Chandran A, Ilhan B, et al. The role of rheumatoid arthritis (RA) flare and cumulative burden of RA severity in the risk of cardiovascular disease. Ann Rheum Dis 2016;75(3):560–5.
71. Kobayashi H, Kobayashi Y, Yokoe I, et al. Magnetic resonance imaging-detected myocardial inflammation and fibrosis in rheumatoid arthritis: associations with disease characteristics and N-terminal pro-brain natriuretic peptide levels. Arthritis Care Res 2017;69(9):1304–11.
72. van Sijl AM, Peters MJ, Knol DK, et al. Carotid intima media thickness in rheumatoid arthritis as compared to control subjects: a meta-analysis. Semin Arthritis Rheum 2011;40(5):389–97.

73. Semb AG, Rollefstad S, Provan SA, et al. Carotid plaque characteristics and disease activity in rheumatoid arthritis. J Rheumatol 2013;40(4):359–68.
74. Akkara Veetil BM, Myasoedova E, Matteson EL, et al. Use of lipid-lowering agents in rheumatoid arthritis: a population-based cohort study. J Rheumatol 2013;40(7):1082–8.
75. Solomon DH, Greenberg J, Curtis JR, et al. Derivation and internal validation of an expanded cardiovascular risk prediction score for rheumatoid arthritis: a Consortium of Rheumatology Researchers of North America Registry Study. Arthritis Rheumatol 2015;67(8):1995–2003.
76. Sparks JA, Chang SC, Liao KP, et al. Rheumatoid arthritis and mortality among women during 36 years of prospective follow-up: Results from the Nurses' Health Study. Arthritis Care Res 2016;68(6):753–62.
77. Reynisdottir G, Karimi R, Joshua V, et al. Structural changes and antibody enrichment in the lungs are early features of anti-citrullinated protein antibody-positive rheumatoid arthritis. Arthritis Rheumatol 2014;66(1):31–9.
78. Stamatelopoulos KS, Kitas GD, Papamichael CM, et al. Subclinical peripheral arterial disease in rheumatoid arthritis. Atherosclerosis 2010;212(1):305–9.
79. Di Minno MN, Ambrosino P, Lupoli R, et al. Clinical assessment of endothelial function in patients with rheumatoid arthritis: a meta-analysis of literature studies.Eur J Intern Med 2015;26(10):835–42.

Crystal-Induced Arthritides in the Elderly: An Update

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KEYWORDS

• Gout • Geriatrics • Treat to target • Comorbidities

KEY POINTS

- The presentation of gout in the elderly includes atypical features and offers more challenges in the differential diagnosis.
- The treatment of gout depends on the stage of the disease, as well as the functional status and comorbidities of the patient.
- Acute gout attacks are disabling and can lead to a substantial decrease in quality of life. Treatment is aimed at quickly resolving pain and inflammation.
- Curative therapy is to dissolve all of the urate deposits by using urate-lowering therapy; when that is accomplished, attacks will no longer occur.

INTRODUCTION

Microcrystalline disease, predominantly monosodium urate (MSU) deposition (gout) is the most common cause of inflammatory arthritis. The prevalence of clinical gout increases with age in both men and women[1] to approximately 8% in men older than the age of 75 years.[2] This increase occurs for several reasons (see later discussion). Gouty arthritis is preceded by hyperuricemia with clinically silent deposition of MSU in and around intraarticular structures, as well as in tendons, bursae, and soft tissues. Deposition of MSU occurs when the serum urate concentration (SUA) exceeds its solubility, which is approximately 6.8 mg/dL. The deposition occurs over years, so it is not surprising that older individuals with hyperuricemia (defined as a SUA >6.8 mg/dL) and, therefore, who have had more time for deposition to occur are at increased risk to develop gouty arthritis, as well as palpable tophaceous deposits (**Fig. 1**). SUA levels

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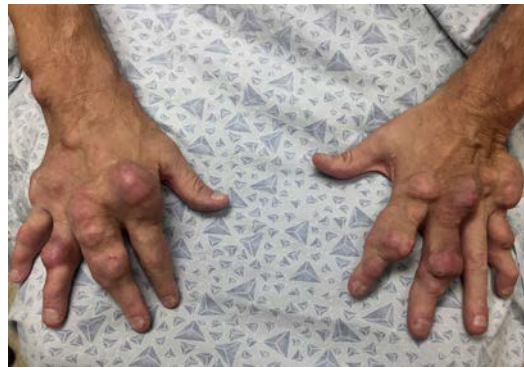

Fig. 1. Large tophaceous deposits affecting multiple fingers.

are higher in humans than in other species due to the genetic absence of uricase. The heterogeneity in SUA levels across populations is due primarily to the variability in genetically determined transport efficiency of excretion of urate by renal (~2/3) and gastrointestinal GI (~1/3) transporters.

Additional contributors to SUA elevations, many of which accompany aging, include obesity, medications (including most diuretics, **Table 1**), decreased glomerular filtration rate, and ingestion of beer (including nonalcoholic) and mineral spirits. Women's SUA levels increase after menopause because estrogen has a uricosuric effect.[3] Although hyperuricemia and gout are strongly associated with insulin resistance, obstructive sleep apnea, hypertension, and the metabolic syndrome, it seems that the independent factor required for gout to develop is sustained hyperuricemia.[4]

Because deposited MSU remains in equilibrium with the SUA, the core principle in treating patients with gout is that maintenance of the SUA significantly below its saturation threshold will ultimately result in the dissolution of the MSU deposits and prevent the occurrence of acute attacks. The lower the level that the SUA is maintained, the more rapid the dissolution of the deposits and the sooner gout attacks will cease. With therapy, the dissolution usually takes months to years to occur and this needs to be considered when making therapeutic decisions in the very elderly. The inverse relationship between rate of resolution and SUA level is the basis of why the ultimate target for SUA in those patients with palpable tophi is lower (<5.0 mg/dL) than those without tophi (<6.0 mg/dL). These tophi presumably reflect a higher total urate burden, which in turn will take longer to dissolve. Whatever the final SUA target, orally dosed urate-lowering therapy (ULT) should generally be initiated at a low dose and slowly escalated to the dose necessary to achieve and maintain the desired SUA. Slow escalation should be prescribed to decrease the chance of a mobilization attack of gout from

Table 1
Drug-induced hyperuricemia

Mechanism	Drugs
Increased uric acid production	Cytotoxic chemotherapy, filgrastim, ribavirin or interferon
Reduced renal clearance of uric acid	Angiotensin-converting enzyme inhibitors, cyclosporine, thiazide and loop diuretics, ethambutol, tacrolimus, low-dose aspirin (mild)
Increased urate production and decreased clearance	Niacin

a sudden decrease in urate level and to perhaps reduce the likelihood of the patient having a (rare) allopurinol hypersensitivity reaction.[5]

Acute gout attacks can be treated successfully with any of several classes of antiinflammatory medications. Corticosteroids, nonsteroidal antiinflammatory drugs (NSAIDs), colchicine, and interleukin (IL)-1 antagonists have all been shown to help resolve gout attacks. The choice of agent is generally dictated by the patient's comorbidities, the potential for adverse interactions with other medications, and personal tolerance of the drugs. Older patients often have several confounding issues, making treatment decisions more complex.

GOUT PRESENTATION IN THE GERIATRIC POPULATION CAN DIFFER FROM CLASSIC GOUT SEEN IN MIDDLE-AGED MEN

Gout in middle-aged and younger men classically presents with recurrent and intermittent attacks in the lower extremity. After menopause, women experience an increase in their SUA owing to the loss of the estrogen's uricosuric effect, which of course can be attenuated by estrogen replacement therapy. For example, in a recent emergency department–based clinical study of acute gout the average age of enrolled subjects was 65 years and 79% were men. Of the participating women in the study, approximately 90% were postmenopausal.[6] As the population ages, the gender disparity of gout narrows. Beyond this observation, there are other incompletely understood differences between how men and women react to hyperuricemia.

The clinical presentation of gout in the elderly includes more patients with atypical features. Joints already damaged by osteoarthritis are seemingly more prone to acute gout. This maybe due in part to decreased local solubility of urate as a result of altered proteoglycan composition. Gout attacks in distal finger joints, as well as tophus formation at the site of Heberden nodes, can be misinterpreted as inflammatory osteoarthritis (**Fig. 2**). This has most frequently been described in postmenopausal women on diuretics but also can occur in men. Some investigators have described an increased frequency of polyarticular attacks in older subjects.[7,8] If more indolent, this type of presentation may mimic rheumatoid arthritis or chronic calcium pyrophosphate (CPP) arthritis pseudogout. Because bacterial septic arthritis is more common in the elderly, this diagnosis must be considered, especially at the time of a first attack. The diagnosis can only be resolved definitively by synovial fluid analysis and culture. In patients with severe dementia, or in patients intubated or sedated postoperatively and who cannot clearly articulate their symptoms, gout attacks may manifest as fever and/or a worsened change in cognitive status. Axial involvement with gout has historically been thought to be uncommon but recent imaging studies indicate that gout can involve the spine. Axial gout has been misdiagnosed as compression fracture, metastatic cancer, and infection.[9,10] These possibilities may not be easily distinguished from tophaceous gout by advanced imaging such as nuclear or MRI scanning.

TREATMENT OF GOUT

The treatment of gout depends on the stage of the disease, as well as the health status and comorbidities, of the patient. Acute attacks need to be diagnosed appropriately and ameliorated promptly to relieve the patient's pain, it is hoped without introducing complications related to the therapy. Particularly in patients who have suffered previous attacks of gout, long-term treatment decisions become paramount in importance. Options include (1) treatment with uric acid–lowering agents, which can both dissolve the excess MSU deposits and prevent further gout attacks; (2) treatment with prophylactic low-dose antiinflammatory medication, such as daily colchicine to reduce the

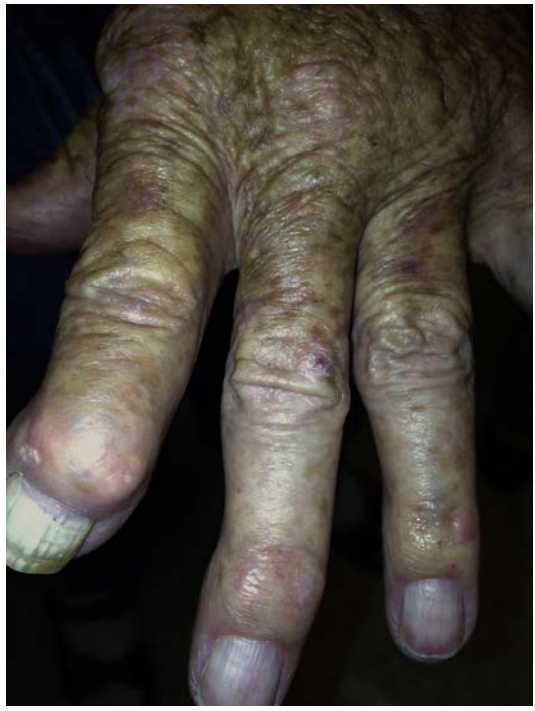

Fig. 2. Tophus on index finger.

number and severity of attacks; and (3) ad hoc treatment of additional attacks when they occur with antiinflammatory medications. Each approach has associated risks and benefits.

MANAGEMENT OF ACUTE GOUT ATTACKS

Treatment of acute attacks is aimed at quickly resolving pain and inflammation. In most cases, the choice of the medication is dictated by the patient's comorbid conditions. There are 4 main groups of medications to treat acute gout attacks: NSAIDs, glucocorticoids (systemic or intraarticular, adrenocorticotrophic hormone), anti–IL-1 (eg, anakinra, an IL-1 receptor antagonist), and colchicine. It must always be kept in mind that treatment of the acute attacks of gout does not address the primary disease process, which is the abnormal deposition of MSU.

NSAIDs are effective and are the traditional gold standard therapy for the treatment of acute gout attacks. All NSAIDs are typically effective when given at full antiinflammatory doses. This includes celecoxib, a cyclooxygenase-2(COX-2) selective NSAID, although higher dosing than usual was used in a trial demonstrating its efficacy (1200 mg load on day 1 followed by 400 mg twice a day, as opposed to 200 mg twice a day).[11] However, NSAID use is potentially associated with several adverse reactions, including acute kidney injury, gastric and intestinal ulcers and bleeding, fluid retention, platelet dysfunction, and headache and confusion (particularly with indomethacin). Virtually all of these complications seem to occur more frequently in the elderly. Several studies suggest a slight increased risk of myocardial infarction or composite cardiovascular adverse outcomes in patients taking NSAIDs other than aspirin. For

these reasons, there has been a trend for physicians to use alternatives to NSAIDs to treat acute gout attacks in the elderly.

Corticosteroids have been used for years to treat attacks of gout, although there are few clinical trials documenting efficacy. A recent pragmatic trial demonstrated equal efficacy of 30 mg per day of prednisolone and indomethacin in treating acute gout.[6] Although prednisone and other antiinflammatory steroids have many well-recognized severe metabolic and other side effects with chronic use, their short-term use may be safer than that of high-dose NSAIDs in treating acute gout attacks. Nevertheless, hyperglycemia, sodium or fluid retention, and various degrees of agitation may occur, and patients and their caregivers should be warned regarding these adverse effects. In a study of 13 subjects, which included 6 older subjects (age range, 66–85 years), gout attacks resolved completely within 7 to 10 days using glucocorticoids. The steroid dose was started at 20 to 50 mg and tapered over a mean duration of 10 days.[12] If possible, steroid therapy should be continued in full dose until the attack resolves, and then tapered to discontinuation over several days (or back to the baseline dose if the patient was taking a steroid chronically). Medrol dose packs (blister packs of a defined dose of a tapering regimen of methylprednisolone pills) can be used to provide simplified instructions. However, sometimes the duration of therapy with dose packs is insufficient and the attack never fully resolves, requiring additional therapy. Intraarticular steroid injections are very effective and their use limits the need for systemic side effects. Infection should be excluded before injection and close follow-up of patients receiving intraarticular injection is necessary. Some anatomic locations are difficult to inject, such as the small joints of the digits and midfoot joints. Intramuscular adrenocorticotrophic hormone is effective but it is expensive and it has essentially the same metabolic side effects as prednisone. The benefits of steroids in terms of avoiding renal and GI complications may be outweighed in some patients by the fluid retention, hyperglycemia, and cognitive effects. Even intraarticular steroids can cause hyperglycemia.

Colchicine has efficacy in relieving the pain and inflammation of acute gout, and low-dose treatment with 3 pills (1.8 mg total) over 24 hours lessened the pain in a clinical study.[13] However, it may not resolve the attack completely, and other analgesic and/or antiinflammatory medications may be required. Some patients have learned that they can abort an impending gout attack if they initiate colchicine therapy as soon as they feel a suspicious twinge. However, for many, perhaps most, other approaches to resolve the attack may be necessary. That being said, chronic low-dose colchicine (0.6–1.2 mg/d) can be effective for prophylaxis against attacks and, if the patient is taking prophylactic colchicine, the dosage should not be changed in the setting of an acute gout attack. However, chronic colchicine must be used with great care, in patients with chronic kidney disease because it is renally excreted.

The primary inflammatory mediator of the acute gout attack is likely IL-1, and specific IL-1 antagonists are strikingly successful at treating and aborting attacks. Several studies now document the impressively rapid response of many (not all) subjects with acute gout in response to treatment with short courses of daily subcutaneous 100 mg doses of anakinra.[14,15] Anakinra is a short-acting, soluble, IL-1 receptor antagonist that has been used successfully in several reports of hospitalized patients, often despite comorbidities limiting the therapeutic options or with prior resistance to corticosteroid therapy. Notably, several patients with successful outcomes had serious infections that were being treated concurrently and/or had recently undergone surgery. Anakinra shares none of the short-term metabolic, renal, or cardiovascular complications of NSAIDs or steroids. Unfortunately, this agent is relatively expensive and it does not presently have a US Food and Drug Administration (FDA) indication for

use in treating gout. In the general rheumatology community, and for older inpatients with multiple comorbidities, this approach to treating inpatients with gout has growing popularity. Patients with very high body mass index may benefit from 200 mg per day instead of 100 mg per day (higher than suggested by the package insert).

Narcotics have variable efficacy in treating the pain of the acute attack and generally should not be relied on as a sole therapy because they do not address the underlying inflammatory process. This is particularly true in the elderly in whom the risk of falling may be significantly increased by the combination of pain from the gout and the central nervous system effects of the narcotics.

PROPHYLACTIC ANTIINFLAMMATORY THERAPY FOR PATIENTS WITH GOUT

Between attacks, patients may be asymptomatic. Unless the serum urate is lowered, urate will continue to deposit in and around joint structures. Definitive curative therapy consists of dissolution of all urate deposits. However, this may take years of oral ULT. An alternative, quality-of-life–driven approach for older individuals is to provide low-dose prophylactic antiinflammatory therapy and only treat attacks as they occur. Low-dose oral colchicine, with appropriate attention to dosing adjustments based on the estimated glomerular filtration rate and potential drug interactions is generally well-tolerated and reasonably effective in many patients for the purpose of reducing the expected frequency of gout flares. This approach may be limited because some patients will experience nausea or diarrhea. More serious complications can arise with chronic ingestion, usually in the setting of decreased renal function and/or with decreased colchicine metabolism owing to effects of other drugs. A painful axonal neuropathy and vacuolar myopathy has been well-described,[16] as has multiorgan failure and death. Several studies have demonstrated pharmacokinetic interactions with colchicine and other drugs, with clarithromycin arguably being the most clinically significant such interaction based on case reports (**Table 2**).[17] Close attention and monitoring of the creatine kinase and blood counts is warranted if the patient is also taking certain statins, ketoconazole, or other drugs that affect the multidrug transporter or the cytochrome P450 system.[18]

In elderly patients with recurrent or tophaceous gout who are otherwise healthy, ULT should be considered. As ULT is introduced, a seeming paradoxic increase in gout attacks (mobilization attacks) may occur. For this reason, antiinflammatory prophylaxis is generally used for approximately 6 months after initiation of the ULT, and

Table 2
Important drug interactions with colchicine and allopurinol

	Drugs That May Interact	Adverse Effects
Colchicine	CYP3A4 inhibitors Strong (clarithromycin, ketoconazole, itraconazole) Moderate (diltiazem, verapamil, erythromycin) P-glycoprotein ABCB1 Cyclosporine, ranozaline, and verapamil	At higher risk of myotoxicity and neurotoxicity, especially with the strong inhibitors (particularly clarithromycin)
Allopurinol	AZA	Myelosuppression owing to increased AZA metabolites (mercaptopurine)
	Warfarin	May increase anticoagulant effects

Abbreviation: AZA, azathioprine.

even longer if tophi are detected on physical examination. Colchicine is used most commonly. Drug levels are not routinely available so empiric dosing is usually 0.6 mg 1 to 2 times per day, with attendant dose adjustments in the setting of renal disease. In colchicine-intolerant patients without relevant comorbidities, low-dose NSAID therapy (ie, naproxen 250 mg daily or bid) may be used to prevent mobilization attacks. This is generally coprescribed with gastric protection. Clinical experience with transplant patients suggests that low-dose prednisone may not be as effective as these other prophylactic agents but sometimes it is the only option.[19] IL-1 antagonism may be an excellent approach to prophylaxis but this is generally limited by cost.

URATE-LOWERING THERAPY

Lowering purine intake, following a heart healthy diet, and avoidance of beer or excessive mineral spirit alcohol ingestion is generally recommended for all patients with gout. A recent cross-sectional analysis of nutrition and serum uric acid in 2 white cohorts of 9734 and 3031 subjects,[20] and an earlier study of 47,150 men, examined the relationship between diet and gout with the SUA.[21] These studies confirmed that consuming meat, seafood, beer, and liquor increases gout risk. Other risk factors identified were consumption of soft drinks sweetened with sugar or fructose, adiposity, hypertension, and diuretic use. In contrast, diets rich in protein, wine, and purine-rich vegetables were not associated with gout flares. Low-fat dairy products may have a protective effect. Weight loss was also found to be protective. Unfortunately, low-purine diets are not very palatable, are difficult to adhere to, and are minimally effective at best, lowering serum urate by only 1 to 2 mg/dL. Thus, medications are generally required to treat hyperuricemia and reduce the SUA to a target level of less than 6 mg/dL, which is a target significantly below the estimated urate saturation point in biological fluids (6.8 mg/dL).

Preventing recurrent gout attacks and tophi formation requires the long-term maintenance of the SUA below the saturation point. This can be achieved by enhancing renal excretion of uric acid (probenecid, lesinurad, losartan), decreasing urate synthesis (allopurinol and febuxostat), or by converting urate to the more soluble metabolite allantoin through the use of enzyme replacement therapy with uricase. Infused pegloticase (every 2 weeks) dramatically reduces the SUA to virtually undetectable levels in the approximately 50% of patients who do not form antipegloticase antibodies.

The lower the SUA, the more rapidly tophi are resolved and the sooner gout attacks will stop. However, some epidemiologic studies now suggest that patients with sustained low serum urate levels may be at increased risk for (and progress more rapidly with) Parkinson disease or vascular or nonvascular dementia.[22] The practical implications of these observations are not yet clear but it may be prudent in those with features of Parkinson disease or mild cognitive impairment to avoid prolonged hypouricemia. In such patients, low SUA can be attained at the outset of treatment to dramatically decrease the urate burden and stop attacks from happening but then the SUA can be allowed to drift up closer to the actual saturation point of 6.8 mg/dL.[23] This concern regarding prolonged hypouricemia must be contrasted with a growing body of data indicating that higher SUA levels contribute to the progression of chronic kidney disease,[24] heart failure, and all-cause mortality.

Currently, the use of uricosuric therapy is limited in the United States. Probenecid has been the major medication for this purpose (losartan and fenofibrate have some uricosuric activity). Probenecid has limited popularity owing to a belief that it has relative limited efficacy and because it may increase the risk for renal stones. In patients with close to normal renal function, who do not excrete more than approximately

800 mg uric acid daily, can drink plenty of fluids, and can alkalinize their urine, it may be efficacious. It can also be used concurrently with a xanthine oxidase inhibitor.

Lesinurad has been approved by the FDA. It is a potent antagonist of the urate reabsorbing transporter urate transporter-1(URAT1) and, when used as mandated by the FDA label along with a xanthine oxidase inhibitor, it is effective at reducing the SUA by approximately an additional 1.5 mg/dL.[25] Nephrolithiasis has not been a problem; however, the occurrence of reversible acute kidney injury was noted in clinical trials, especially when a xanthine oxidase inhibitor was not used concurrently. These reversible episodes of acute kidney injury might be owing to acute urate tubular nephropathy.

Allopurinol (100-mg and 300-mg tablets) is the most widely used xanthine oxidase inhibitor. Most physicians prescribe no greater than 300 mg per day. However, this dosage has been demonstrated to reduce the serum urate to less than 6 mg/dL in fewer than 30% of patients.[26] Allopurinol has been approved by the FDA for doses up to 800 mg per day. Guidelines from the British Society of Rheumatology advocate a maximum dose of 900 mg per day. It should be noted that these maximum doses are based on limited data and not on documented toxicity. Slow upward titration, starting with 50 to 100 mg per day at the initiation of therapy, is the commonly recommended regimen. Although GI intolerance is a common problem, it is more likely that concern about the rare but extremely severe hypersensitivity reaction (approximately 25% mortality) has contributed to its underuse and underdosing, particularly in the setting of chronic kidney disease. This rare complication happens approximately 3 to 9 times in 1000 patients (the higher estimate likely occurring in patients with chronic kidney disease). It has not been demonstrated that reduction of the target dose will decrease the frequency of hypersensitivity but the initiation at a low dose, with a very slow dose escalation, may reduce the hypersensitivity reaction risk,[5] which may be more frequent in Chinese and some other Asian groups.

Febuxostat (40-mg and 80-mg tablets) is an oral nonpurine selective inhibitor of xanthine oxidase. In the Febuxostat versus Allopurinol Controlled Trial (FACT), a 52-week randomized, double-blind study in hyperuricemic subjects with gout, serum urate levels were reduced to less than 6.0 mg/dL in more than 50% of subjects receiving febuxostat 80 mg or 120 mg once daily compared with only 21% of subjects receiving a 300-mg fixed dose of allopurinol who were observed to achieve this goal.[27] This does not imply that allopurinol at higher doses would not be equally effective (no allopurinol dose escalation was done in the trial). Indeed, dose escalation of allopurinol is successful in lowering the SUA to a target of less than 6 mg/dL in almost all subjects.[28]

Because allopurinol and febuxostat are not similar in chemical structure, febuxostat is an attractive alternative in patients allergic to allopurinol. This has been studied in a limited number of subjects.[29] Febuxostat remains far more expensive in the United States than allopurinol. Lesinurad, which is also expensive, or probenecid can be added to either of these medications to improve their efficacy. However, even with the combination of a uricosuric and a xanthine oxidase inhibitor, it may be difficult to profoundly lower the SUA in select individuals.

Uricase metabolizes urate to the more soluble molecule allantoin, which is excreted in the urine. Humans evolutionarily deactivated uricase centuries ago and thus have higher SUA than most other species. Pegloticase is a recombinant polyethylene glycol conjugated uricase that is FDA approved for intravenous therapy for gout in patients who have failed other ULTs. It rapidly and profoundly reduces serum urate to less than 0.5 mg/dL in most patients and can lead to resolution of tophi over months.[30] A predictable side effect of rapidly and dramatically reducing SUA is the occurrence of severe gout flares, despite using prophylactic therapy. Pegloticase is administered by intravenous infusion every 2 weeks; this can be decreased to every 3 weeks in many responder patients. However, most patients develop some antimedication

antibodies, most to the polyethylene glycol coating. Those patients with very high titer antibody levels rapidly become drug-resistant and experience the almost all of the infusion reactions, which are usually mild.[31] By checking the SUA before each infusion, most infusion reactions can be predicted and prevented by discontinuing therapy. In the approximately 50% of patients who experience an ongoing dramatic lowering of SUA, therapy can be continued until visible tophi are resolved and attacks cease. At that point (or even before) the pegloticase can be stopped and the patient switched back to an oral agent targeting the SUA to a level less than 6 mg/dL.

CALCIUM PYROPHOSPHATE ARTHRITIS

CPP arthritis is less common than gout. The most recognized manifestation is an acute attack, often in the wrist or the knee, which resembles an acute gout attack and can only be reliably distinguished from gout by synovial fluid analysis. There are far fewer clinical trials and studies of subjects with CPP deposition disease (CPPD),[32] so the management of acute attacks is nearly identical to that of patients with gout. That being said, there are limited data to suggest efficacy of hydroxychloroquine or methotrexate in patients with CPP arthritis. A diagnosis of CPPD warrants excluding an underlying endocrinopathy such as hyperparathyroidism. Otherwise, for the management of the disease, there is no accepted approach to reducing crystal deposition akin to urate dissolution therapy. CPPD may manifest by chondrocalcinosis (often asymptomatic) or the finding of crystals at the time of arthroplasty. These presentations are common in patients with longstanding osteoarthritis and thus not uncommon in the elderly. Chronic CPPD can result in an indolent inflammatory arthritis, often with wrist and metacarpophalangeal joint involvement, which can mimic rheumatoid arthritis. The 2 conditions can sometimes be distinguished radiographically or by finding calcium crystals in the synovial fluid. A specific clinical syndrome of fever, neck pain, and pseudomeningitis occurs with acute CPP arthritis of the neck (crowned dens syndrome).[33]

SUMMARY

Gout is a chronic disease of deposition of MSU in multiple anatomic locations. Although the major attributed manifestation is the acute gout flare, which must be treated promptly, ideal long-term management requires dissolution of the urate deposition by lowering the serum urate to less than 6.0 mg/dL to ultimately stop flares and prevent the development of a chronic arthropathy, and perhaps worsening or progression of other urate associated metabolic conditions, including chronic kidney disease. The decisions surrounding the initiation or intensification of ULT must be individualized, especially in elderly patients. The decision process must include evaluation of the patient's life expectancy, frequency and impact of gout flares, daily function, comorbidities, baseline medications, and the ability to tolerate ULT, gout flare prophylaxis, and the repetitive treatment of the acute flares.

REFERENCES

1. Zhu Y, Pandya BJ, Choi HK. Prevalence of gout and hyperuricemia in the US general population: the National Health and Nutrition Examination Survey 2007-2008. Arthritis Rheum 2011;63:3136–41.
2. Mikuls TR, Farrar JT, Bilker WB, et al. Suboptimal physician adherence to quality indicators for the management of gout and Rheumatology asymptomatic hyperuricemia: results from the UK General Practice Research Database (GPRD). Rheumatology (Oxford) 2005;44(8):1038–42.

3. Nicholls A, Snaith ML, Scott JT. Effect of oestrogen therapy on plasma and urinary levels of uric acid. Br Med J 1973;1:449–51.
4. Duskin-Bitan H, Cohen E, Goldberg E, et al. The degree of asymptomatic hyperuricemia and the risk of gout. A retrospective analysis of a large cohort. Clin Rheumatol 2014;33:549–53.
5. Stamp LK, O'Donnell JL, Zhang M, et al. Using allopurinol above the dose based on creatinine clearance is effective and safe in patients with chronic gout, including those with renal impairment. Arthritis Rheum 2011;63(2):412–21.
6. Rainer TH, Cheng CH, Janssens HJ, et al. Oral prednisolone in the treatment of acute gout. Ann Intern Med 2016;164:464–71.
7. Fam AG. Gout in the elderly. Clinical presentation and treatment. Drugs Aging 1998;13:229–43.
8. Meyers OL, Monteagudo FSE. A comparison of gout in men and women: a 10-year experience. S Afr Med J 1986;70:721–3.
9. Saketkoo LA, Robertson HJ, Dyer HR, et al. Axial gouty arthropathy. Am J Med Sci 2009;338:140–6.
10. Konatalapalli RM, Lumezanu E, Jelinek JS, et al. Correlates of axial gout: a cross-sectional study. J Rheumatol 2012;39:1445–9.
11. Schumacher HR, Berger MF, Li-Yu J, et al. Efficacy and tolerability of celecoxib in the treatment of acute gouty arthritis: a randomized controlled trial. J Rheumatol 2012;39:1859–66.
12. Groff GD, Franck WA, Raddatz DA. Systemic steroid therapy for acute gout: a clinical trial and review of the literature. Semin Arthritis Rheum 1990;19:329–36.
13. Terkeltaub RA, Furst DE, Bennett K, et al. High versus low dosing of oral colchicine for early acute gout flare: twenty-four-hour outcome of the first multicenter, randomized, double-blind, placebo controlled, parallel-group, dose-comparison colchicine study. Arthritis Rheum 2010;62:1060–8.
14. Ghosh P, Cho M, Rawat G, et al. Treatment of acute gouty arthritis in complex hospitalized patients with anakinra. Arthritis Care Res 2013;65(8):1381–4.
15. Thueringer JT, Doll NK, Gertner E. Anakinra for the treatment of acute severe gout in critically ill patients. Semin Arthritis Rheum 2015;45(1):81–5.
16. Kuncl RW, Duncan G, Watson D, et al. Colchicine myopathy and neuropathy. N Engl J Med 1987;316:1562–8.
17. Hung IF, Wu AK, Cheng VC, et al. Fatal interaction between clarithromycin and colchicine in patients with renal insufficiency: a retrospective study. Clin Infect Dis 2005;41:291–300.
18. Terkeltaub RA, Furst DE, DiGiacinto JL, et al. Novel evidence based colchicine dose reduction algorithm to predict and prevent colchicine toxicity in the presence of cytochrome P450 3A4/P glycoprotein inhibitors. Arthritis Rheum 2011;63:2226–37.
19. Clive DM. Renal transplant-associated hyperuricemia and gout. J Am Soc Nephrol 2000;11:974–9.
20. Zykova SN, Storhaug HM, Toft I. Cross-sectional analysis of nutrition and serum uric acid in two Caucasian cohorts: the AusDiab Study and the Tromsø study. Nutr J 2015;14:49.
21. Choi HK, Atkinson K, Karlson EW, et al. Purine-rich foods, dairy and protein intake, and the risk of gout in men. N Engl J Med 2004;350:1093–103.
22. Hong JY, Lan TY, Tang GJ, et al. Gout and the risk of dementia: a nationwide population-based cohort study. Arthritis Res Ther 2015;17:139–46.

23. Perez-Ruiz F, Herrero-Beites AM, Carmona L. A two staged approach to the treatment of hyperuricemia in gout: the “dirty dish” hypothesis. Arthritis Rheum 2011; 63:4002–6.
24. Levy G, Cheetham TC. Is it time to start treating asymptomatic hyperuricemia? Am J Kidney Dis 2015;66:933–5.
25. Hoy S. Lesinurad: first global approval. Drugs 2016;76:509–16.
26. Perez-Ruiz F, Alonso-Ruiz A, Calabozo M, et al. Efficacy of allopurinol and benzbromarone for the control of hyperuricaemia. A pathogenic approach to the treatment of primary chronic gout. Ann Rheum Dis 1998;57:545–9.
27. Becker MA, Schumacher HR Jr, Wortmann RL, et al. Febuxostat compared with allopurinol in patients with hyperuricemia and gout. N Engl J Med 2005;353: 2450–61.
28. Reinders MK, Haagsma C, Jansen TL, et al. A randomised controlled trial on the efficacy and tolerability with dose escalation of allopurinol 300–600 mg/day versus benzbromarone 100–200 mg/day in patients with gout. Ann Rheum Dis 2009;68:892–7.
29. Chohan S. Safety and efficacy of febuxostat treatment in subjects with gout and severe allopurinol adverse reactions. J Rheumatol 2011;38(9):1957–9.
30. Baraf H, Becker M, Gutierrez-Urena S, et al. Tophus burden reduction with pegloticase: results from phase 3 randomized trials and open-label extension in patients with chronic gout refractory to conventional therapy. Arthritis Res Ther 2013;15: R137.
31. Lipsky P, Calabrese L, Kavanaugh A, et al. Pegloticase immunogenicity: the relationship between efficacy and antibody development in patients treated for refractory chronic gout. Arthritis Res Ther 2014;16:R60.
32. Rosenthal AK, Ryan LM. Calcium pyrophosphate deposition disease. N Engl J Med 2016;374:2575–84.
33. Godfrin-Valnet M, Godfrin G, Godard J, et al. Eighteen cases of crowned dens syndrome: Presentation and diagnosis. Neurochirurgie 2013;59:115–20.

Lumbar Spinal Stenosis in Older Adults

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KEYWORDS

• Lumbar spinal stenosis • Low back pain • Magnetic resonance imaging
• Decompression surgery • Epidural steroid injection

KEY POINTS

- Lumbar spinal stenosis is a common problem among older adults, and the prevalence increases with age.
- Consensus has been reached to define and diagnose clinical questions and radiologic criteria for lumbar spinal stenosis.
- MRI is the diagnostic modality of choice for the evaluation of lumbar spinal stenosis.
- Radiographic evidence of lumbar spinal stenosis is quite prevalent, although such findings may not correlate well with symptoms of lumbar spinal stenosis.
- Conservative and surgical therapies are available; however, recommendations specific to the elderly population are difficult to sparse high-quality randomized clinical trials.

INTRODUCTION

Lumbar spinal stenosis (LSS) is one of the most common pathologic conditions to cause low back pain (LBP) among the elderly. A narrowing of any part of the spinal canal or spinal vertebrae places unusual pressure on the spinal cord and the nerve roots, and painful symptoms are usually the result. LBP and LSS follow similar trends, in general. LBP is present in up to 70% of adults aged 60 years or older, and its incidence increases with advancing age.[1] An increasingly aging population warrants further vigilance among clinicians to be familiar with causes of LBP in general and with the management of LSS.

Spinal stenosis can be classified by the region of the spine affected: cervical, thoracic, and lumbar. The lumbar region is the most common area of the spine affected, followed by the cervical region. Spinal stenosis can further be classified as acquired (as a result of disease or injury) or rarely, congenital; usually with symptoms starting before the age of 50, undetectable at birth, and usually nonpreventable. This review largely focuses on acquired causes of LSS.

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EPIDEMIOLOGY

Spinal stenosis is highly prevalent in older adults older than 60 years of age.[2,3] There is increasing prevalence among women with age, although men outnumbered women in the 50 to 60 and 60 to 69 age groups.[2,4] The prevalence of spinal stenosis in Japan was estimated to be about 5.7% to 10%,[2,4] and in the United States about 22.5%.[3]

CAUSES, ASSOCIATIONS

Spinal stenosis in the elderly may result from lumbar degenerative spondylolisthesis, particularly when it is accompanied by facet joint hypertrophy and thickening of the ligamentum flavum.[1] In turn, this may lead to unilateral or bilateral radiculopathy and neurogenic claudication. In general, degenerative spine disorders and other arthritic conditions, compression deformities, congenital spine disorders, tumors, trauma, Paget's disease, fluorosis with secondary ossification, calcium deposits, and other conditions leading to herniated discs, and thickened ligaments can cause spinal stenosis. Diffuse idiopathic skeletal hyperostosis has been associated with LSS.[5]

LSS was associated with certain comorbid conditions, such as diabetes mellitus, urologic disorders, osteoarthritis, fracture, and depression.[2] Obesity, a high waist circumference, and a positive family history of LBP were found to be highly associated with symptoms of LSS with radiographic findings.[6]

DIAGNOSIS

History and Physical Examination

A landmark study using the Delphi method achieved a consensus-based set of history-based items that act as a pragmatic set of criterion for defining and diagnosing LSS in clinical and research settings (**Box 1**, Section A).[7] Within the first 6 questions, there was 80% certainty of LSS diagnosis. Consensus was achieved among 279 musculoskeletal medicine clinicians, including 3 rheumatologists. Furthermore, clinical criteria independently associated with neurogenic claudication due to LSS were identified; namely, age greater than 60 years, positive 30-second extension test, negative straight leg test, pain in both legs, leg pain relieved by sitting, and leg pain decreased by leaning forward or flexing the spine.[8]

Symptoms of LBP are highly associated with spinal stenosis.[3] Myelopathic symptoms can ensue as a result of cord and nerve root compromise. There are other common causes of LBP among the elderly. Attempts to distinguish clinical findings of lumbar disc herniation from LSS have shown that the former is associated more with greater leg pain intensity, disability, and anterior leg pain, whereas the latter is associated with normal trunk flexion, absence of nerve root tension signs, and abnormal Achilles reflexes.[9] Many studies have been done to evaluate the usefulness of various physical examination evaluations for determination of LSS diagnosis and severity. The 3-Minute Sitting test is useful in evaluating lumbar foraminal stenosis.[10] Tibial Nerve Compression Test is useful for LSS diagnosis in a primary care setting.[11] A lumbar extension-loading test can determine the involved spinal level.[12] Measures of walking capacity included within the Physical Function Scale of the Swiss Spinal Stenosis Questionnaire, the Oswestry Disability Index (ODI, a questionnaire that quantifies disability for LBP), and a self-reported walking capacity change score are helpful.[13]

The North American Spine Society (NASS) established evidence-based clinical guidelines on the Diagnosis and Treatment of Degenerative Lumbar Spinal Stenosis (revised 2011). Because many cases of LSS are associated with spondylolisthesis,

Box 1
Historical and radiologic criteria for lumbar spinal stenosis

A. 2016 Consensus on the history factors to consider for the diagnosis of lumbar spinal stenosis

History factors to consider

1. Does the patient have buttock pain while walking?
2. Does the patient flex forward to relieve symptoms?
3. Does the patient feel relief when using a shopping cart or bicycle?
4. Does the patient have motor or sensory disturbance while walking?
5. Are the pulses in the foot present and symmetric?
6. Does the patient have lower extremity weakness?
7. Does the patient have low back pain?

B. 2014 Consensus on radiologic parameters (core items) for structured reporting on lumbar spinal stenosis

Central stenosis

1. Compromise of the central zone
2. Relation between fluid and cauda equina

Lateral stenosis

1. Nerve root compression in the lateral recess

Foraminal stenosis

1. Nerve root impingement
2. Compromise of the foraminal zone

Data from Tomkins-Lane C, Melloh M, Lurie J, et al. ISSLS Prize Winner: consensus on the clinical diagnosis of lumbar spinal stenosis: results of an International Delphi Study. Spine (Phila Pa 1976) 2016;41(15):1239–46; and Andreisek G, Deyo RA, Jarvik JG, et al; LSOS Working Group. Consensus conference on core radiological parameters to describe lumbar stenosis—an initiative for structured reporting. Eur Radiol 2014;24(12):3224–32.

the NASS has also set forth recommendations: Diagnosis and Treatment of Degenerative Spondylolisthesis (revised 2014).[14,15]

IMAGING

There are multiple imaging and diagnostic modalities available to evaluate LSS (**Table 1**); however, clear gold-standard diagnostic criteria have yet to be established. Among the available studies, MRI without contrast is the modality of choice to verify the presence of spinal canal narrowing or nerve root compression.[16,17]

Imaging is a mainstay in the evaluation of spinal stenosis. However, medical decision making relies heavily on the clinical acumen of the physician in consideration of symptoms, imaging findings, and risks of therapeutic options.

Plain Radiography

Plain radiography may demonstrate abnormalities suggestive of lumbar stenosis, including spondylolisthesis, disk-narrowing, facet-joint hypertrophy, end-plate sclerosis,

Table 1
Imaging options for spinal stenosis

Modality	Comments
Plain radiography	Limited in anatomic detail Can demonstrate findings suggestive of possible spinal stenosis
CT scan	Better for evaluation of bony structures Findings of spinal stenosis include: reduced cross-sectional area of canal and neural foramina caused by various causes, including disk protrusion, hypertrophy of ligamentum flavum, hypertrophy of facet joints, osteophytes Use of MRI or CT myelogram contraindicated
CT with myelogram	Myelogram helps to improve visualization of bony detail and nerve root Useful when MRI contraindicated Invasive, requires contrast, has complications Similar diagnostic accuracy as MRI
MRI	Diagnostic test of choice Best test to evaluate soft tissue, bony anatomy, neuroanatomy

and neural foraminal osteophytes.[18] Plain radiographs are limited in anatomic detail and lacking in assessment of soft tissue and spinal cord.[19]

Computed Tomography Scan

Computed tomography (CT) scan is especially useful if bony anatomy needs to be closely assessed. Findings suggestive of LSS include reduced cross-sectional area of canal and neural foramina caused by various causes, including disk protrusion, hypertrophy of ligamentum flavum, hypertrophy of facet joints, and osteophytes.[18] Such imaging is generally used if CT myelography or MRI is contraindicated or inconclusive.[16]

Computed Tomography Myelography

CT myelography is performed for closer assessment of neural structures and has demonstrated comparable diagnostic accuracy to MRI. The study is invasive, requires the need for contrast, and has risk of complications, including nerve injury, bleeding around nerve roots, and, rarely, seizures.[17] Therefore, this modality should be used when MRI is contraindicated (such as in patients with pacemakers or severe claustrophobia).[16]

MRI

MRI (without contrast) is the most promising diagnostic tool because it provides appropriate detail into soft tissues, bony anatomy, neuroanatomy, including nerve roots, conus medullaris, and spinal cord (**Fig. 1**).[17]

When comparing the diagnostic accuracy of imaging modalities for evaluating LSS, large discrepancies in sensitivity and specificity are noted with the use of MRI as the generally accepted modality of choice.[17]

Consensus criteria to diagnose LSS radiologically have been developed (see **Box 1**, Section B).[20] Radiologic parameters to describe central, lateral, and foraminal stenosis were developed. Prior attempts covering MRI-based criteria to describe and diagnose LSS included measurement of the following: cross-sectional area of the dural sac,[21] anteroposterior spinal canal diameter,[22] and canal stenosis grading (ratio: cerebrospinal fluid/rootlet).[23] However, there is a lack of clear correlation between narrower measurements and severity of pain,[24] and there is considerable variability in interreader and intrareader agreement of commonly used quantitative and qualitative image parameters.[25]

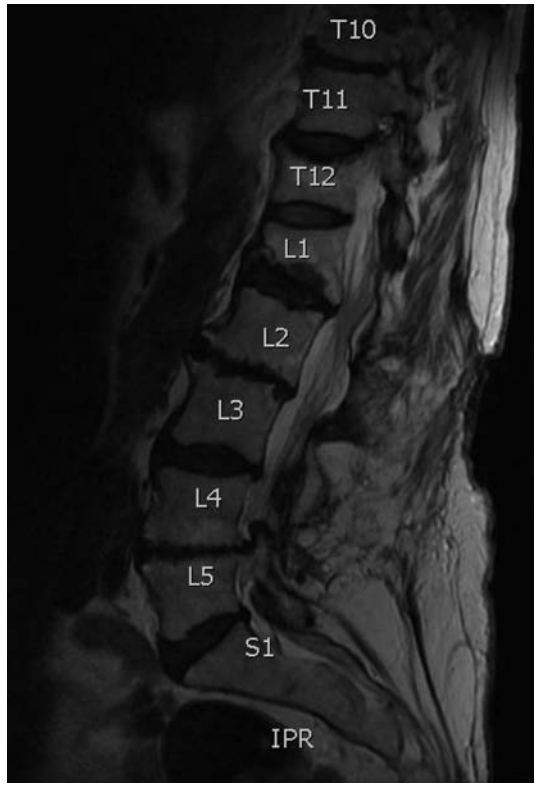

Fig. 1. Sagittal T2-weighted image, MRI of the lumbar spine shows mild central spinal stenosis at L1-2 and L3-4. There is preservation of anatomic alignment, postsurgical changes relating to prior hemilaminectomies at L2-3 and L4-5, compression deformities at T12 and L1. Axial images (not shown here) show at L1-2 a posterior disc osteophyte complex, with the thecal sac measuring 8 mm in midline anteroposterior (AP) diameter, with clumping of the cauda equina. At L3-4, there is a small posterior disc bulge, with the thecal sac measuring 9 mm in midline AP diameter, with clumping of the cauda equina fibers at this level. IPR, inpatient rehabilitation. The remainder of the bone marrow appears homogenous. The distal spinal cord is normal in signal and morphology and the conus medullaris terminates at L1.

In addition, incidental radiologic findings of high-grade LSS may be present in individuals who are completely asymptomatic.[26] Studies have suggested a 20% prevalence of some degree of spinal stenosis on imaging in adults older than 60 years of age who have no symptoms or major limitations.[18] It is important to note that the presence of radiographic findings of LSS may not necessarily correlate with symptoms of LSS. In a 2013 population-based study, only 17.5% of patients with severe LSS were symptomatic.[27] Therefore, it is important to interpret imaging findings in conjunction with clinical severity and physical examination findings.

Other Diagnostic Modalities

Self-administered questionnaires

Self-administered questionnaires have also been used as diagnostic support tools and are thought to improve accuracy of diagnosis and of the classifying of severity of symptoms or even predicting postoperative improvement. Various questionnaires

used widely in LSS literature include Roland-Morris Disability Questionnaire (RMDQ), ODI, visual analog scale (VAS), EQ-5D, and EQ-VAS. However, at present there remains insufficient evidence to use questionnaires for diagnostic purposes.[16]

Electromyography and nerve conduction studies

Electromyography (EMG) and nerve conduction studies (NCS) are not useful tools for diagnosing LSS.[18] At times, they are used to explore differential diagnoses (peripheral neuropathy) and underlying issues, such as superimposed radiculopathy. The sensitivity of EMG was 63%, and for NCS, 54%. The combined accuracy of EMG and NSC is only modest,[17] with a sensitivity of 79%.[28]

Other tests include *dermatomal somatosensory-evoked potentials and assessment of caudal motor conduction time with magnetic stimulation.* A systematic review showed that the diagnostic accuracy of electrodiagnostic testing was inferior to MRI.[17]

Paraspinal mapping

Paraspinal mapping has a high specificity (92%–100%) and has been shown to confirm the diagnosis of degenerative LSS in patients with mild to moderate symptoms and imaging findings suggesting of LSS.[29]

TREATMENT

Treatment recommendations specific to the elderly population are not available because of lack of high-quality studies.[30]

Conservative Therapy

Pharmacologic management

Pharmacologic management of LSS, in general, includes the use of acetaminophen, nonsteroidal anti-inflammatory medications (NSAIDs), aspirin, gabapentin, pregabalin, limaprost (an oral prostaglandin E1 derivative) and low-dose narcotic medications. All of these medications must be used with caution in the elderly population given their side-effect profiles especially in respect to neurologic, renal, gastrointestinal, and cardiovascular events. It is important to note that evidence is lacking in the use of these medications specifically for spinal stenosis. A systematic review and meta-analysis investigating the use of calcitonin for LSS showed no significant improvement in symptom control nor improvement in walking distance.[31]

Studies on gabapentin, although showing efficacy in reducing pain, are largely limited by nonrandomization, low subject numbers, and short study periods.[32,33]

Physical therapy, stretching, and aerobic exercise routines

Physical therapy, stretching, and aerobic exercise routines are some of the regimens that are implemented as initial conservative strategies in the treatment of LSS. Goals of physical therapy and exercise should be aimed at strengthening core muscles to improve posture and increase stabilization. Improving lumbar flexion and reducing lumbar lordosis may also help improve pain. Other exercise regimens include low-intensity bicycling, physiotherapy, and ergonomic training.

A trial comparing 3 groups (ultrasound in continuous mode on back muscles with exercise vs sham ultrasound with exercise vs placebo without ultrasound and without exercise) showed significantly decreased leg pain and decrease in disability score in those receiving exercise with and without ultrasound at 3 weeks. There was also a significantly lower amount of analgesic use in the groups that had actual and sham ultrasound therapy compared with the placebo group.[34]

A randomized controlled trial evaluating the benefit of presurgery *physiotherapy* (for 9 weeks) versus control (patients received standardized information about surgery) showed a significant decrease in ODI, visual analog scale (VAS) for back and leg pain, EQ-5D (a tool to measure quality of life), EQ-VAS (visual analog scale for recording an individual's rating of current quality-of-life state), and physical component score compared with baseline.[35]

Epidural Steroid Injections

Current evidence does not strongly support epidural steroid injections (ESI) for *long-term* relief of neurogenic claudication. Guidelines state although there is evidence that nonfluoroscopically guided interlaminar and single-radiographically guided transforaminal ESIs can result in short-term symptom relief in patients with neurogenic claudication or radiculopathy, there is conflicting evidence concerning long-term efficacy.[15] Transforaminal ESI was evaluated in an observational study and was found to be a reasonable treatment of LSS and can be an alternative to surgery.[36] Multiple small noncontrolled trials have shown short-term pain relief.[37] However, in a large randomized controlled trial of 400 patients with moderate to severe leg pain (self-reported pain score of 4 or greater on a scale of 0–10) and disability (score of 7 or higher on the RMDQ [range 0–24]), there were no statistically significant differences between ESI versus epidural lidocaine.[38] A double-blind randomized trial showed that ESI offered no significant relief of pain over gabapentin among patients with lumbosacral radicular pain due to spinal stenosis or herniated disc.[39]

Other conservative therapies being studied include transforaminal balloon adhesiolysis, which was thought to be successful in improving symptoms in patients with chronic lumbar foraminal stenosis due to degenerative disc herniation.[40]

Surgical Therapy

Decompressive laminectomy

Decompressive laminectomy is the removal of part or all of the lamina, to create more space in the spinal canal and to relieve pressure on the cord. It is the preferred surgical technique in older adults because it is the more conservative procedure and has lower complication rates.[41,42]

Decompression with fusion

Decompression with fusion was the method of choice for spinal stenosis patients *with spondylolisthesis*.[43] However, rates of decompression with fusion have increased in the United States in the last decade in LSS patients, with or without spondylolisthesis.[44] Decompression with fusion did not result in better outcomes (6-minute walk test, ODI, health economic evaluation) at 2 and 5 years, as compared with decompression alone.[45] Moreover, the addition of fusion to decompression increases the risk of complications and is associated with more perioperative blood loss and longer surgical time.[41] Another study evaluating Medicare claims between 2002 and 2007 redemonstrated the higher frequency of complex fusion surgeries as well as an increase in major complications, 30-day mortality, and resource use.[46]

Interspinous spacing device implantation

Interspinous spacing device implantation is a less invasive technique favored in patients with spinal stenosis *without spondylolisthesis*. A device is placed between the spinous processes of affected vertebra, which helps relieve compression. In a cohort analysis evaluating 99,084 Medicare patients aged 66 years and older with LSS who received surgical intervention, patients receiving interspinous spacing device implantation were significantly older than those who underwent

decompression or fusion. Compared with invasive surgical techniques, the spacing device had fewer complications but higher rates of revision surgery (16.8% at 2 years).[47] Several other interspinous process devices have been developed are being studied in terms of complications, device failure, reoperation rates, symptom relief, and outcomes, as compared with first-generation devices. A recent study found a lower reoperation rate at 24 months with the newer-generation devices (3.7%) as compared with the older devices (11.1%).[48]

Older individuals (age 80 and older) undergoing surgery experience improvement in outcomes similar to the younger population. However, there is conflicting literature regarding the higher risk of complications. In multiple studies, the older population had a higher rate of minor and major complications, longer hospital stays, and more in-hospital mortality.[49–51]

A *Cochrane Review* showed a paucity of evidence on the efficacy of surgery for LSS.[52] There are no trials that have compared surgery with no treatment, placebo, or sham surgery. Decompression plus fusion and interspinous process spacers were deemed not to be superior to conventional decompression alone.

Surgical Therapy Versus Conservative Treatment

A *Cochrane Review* assessing the effectiveness of different types of surgery compared with different types of nonsurgical interventions in adults with symptomatic LSS showed no observable clear benefits with surgery versus nonsurgical treatment, except for the higher risk of side effects (up to 24%) in surgical cases.[53]

According to guideline recommendations, conservative nonsurgical therapy should be exhausted before considering surgery. Patients with *mild* symptoms may be treated conservatively,[16] whereas patients with *moderate to severe* symptoms of neurogenic claudication may benefit from decompression. This issue is complicated by the lack of clear definition of intensity of symptoms (mild vs moderate vs severe). Although some clinicians used patient-reported pain and quality-of-life questionnaires, others may assess severity idiosyncratically or based upon the effect on quality of life in conjunction with severity of imaging findings.

In a randomized controlled study evaluating decompression compared with nonoperative management (NSAIDs and physiotherapy), operative treatment was more effective in reducing self-reported leg and back pain and improving functional ability (based on ODI) at 6-month, 1-year, and 2-year follow-up. However, it is important to note that the nonoperative group showed statistically significant improvement in walking ability (assessed via questionnaire and treadmill evaluation) throughout the 2-year follow-up.[54]

A long-term 8- to 10-year study comparing outcomes between surgical and nonsurgical management demonstrated that at 1- and 4-year follow-up, outcomes favored surgical treatment; however, at 8- and 10-year follow-up, a similar percentage of surgical and nonsurgical patients reported that their back pain was improved and that they were satisfied with their current status.[55]

Moreover, studies have compared physical therapy regimens and rehabilitation programs to surgery and have demonstrated similar outcomes.[56,57]

A prospective multicenter randomized controlled clinical trial involving 26 interventional pain management centers assessing improvement in function and pain for Medicare beneficiaries receiving minimally invasive lumbar decompression (MILD) versus ESI showed that at 1-year follow-up, MILD was statistically superior to ESI in the treatment of LSS with neurogenic claudication and verified central stenosis due to ligamentum flavum hypertrophy.[58]

SUMMARY

LSS is a frequent cause of LBP among adults and may be due to several conditions. Despite the utility of MRI or CT, radiographic evidence of LSS may not correlate well with symptoms. An increase in utilization of surgery has been noted, although surgery has shown no significant benefit over more conservative options. Ultimately, the decision to pursue surgical intervention should require a well-thought-out interdisciplinary effort by identifying comorbidities and possible risks of various surgical options depending on their invasiveness, quality of life, and severity of symptoms.

REFERENCES

1. Wong AYL, Karppinen J, Smartzis D. Low back pain in older adults: risk factors, management options and future directions. Scoliosis Spinal Disord 2017;12:14.
2. Yabuki S, Fukumori N, Takegami M, et al. Prevalence of lumbar spinal stenosis, using the diagnostic support tool, and correlated factors in Japan: a population-based study. J Orthop Sci 2013;18:893–900.
3. Kalichman L, Cole DH, Li L, et al. Spinal stenosis prevalence and association with symptoms: Framingham study. Spine J 2009;9(7):545–50.
4. Ishimoto Y, Yoshimura N, Muraki S, et al. Prevalence of symptomatic lumbar spinal stenosis and its association with physical performance in a population-based cohort in Japan: the Wakayama Spine Study. Osteoarthritis Cartilage 2012;20:1103–8.
5. Yamada K, Satoh S, Hashizume H, et al. Diffuse idiopathic skeletal hyperostosis is associated with lumbar spinal stenosis requiring surgery. J Bone Miner Metab 2018. [Epub ahead of print].
6. Doualla-Bija M, Takang MA, Mankaa E, et al. Characteristics and determinants of clinical symptoms in radiographic lumbar spinal stenosis in a tertiary health care centre in sub-Saharan Africa. BMC Musculoskelet Disord 2017;18(1):494.
7. Tomkins-Lane C, Melloh M, Lurie J, et al. ISSLS Prize Winner: consensus on the clinical diagnosis of lumbar spinal stenosis: results of an International Delphi Study. Spine (Phila Pa 1976) 2016;41(15):1239–46.
8. Genevay S, Courvoisier DS, Konstantinou K, et al. Clinical classification criteria for neurogenic claudication caused by lumbar spinal stenosis. The N-CLASS criteria. Spine J 2017 [pii:S1529-9430(17)31052-5].
9. Rainville J, Lopez E. Comparison of radicular symptoms caused by lumbar disc herniation and lumbar spinal stenosis in the elderly. Spine (Phila Pa 1976) 2013;38(15):1282–7.
10. Mizuno T, Sakakibara T, Kasai Y. Three-minutes sitting test for evaluating lumbar foraminal stenosis: a preliminary report. J Spinal Cord Med 2018;1–4.
11. Adachi S, Nakano A, Kin A, et al. The tibial nerve compression test for the diagnosis of lumbar spinal canal stenosis—a simple and reliable physical examination for use by primary care physicians. Acta Orthop Traumatol Turc 2017 [pii:S1017-S1995X(16)30143-2].
12. Takahashi N, Kikuchi S, Yabuki S, et al. Diagnostic value of the lumbar extension-loading test in patients with lumbar spinal stenosis: a cross-sectional study. BMC Musculoskelet Disord 2014;15:259.
13. Tomkins-Lane CC, Battie MC, Macedo LG. Longitudinal construct validity and responsiveness of measures of walking capacity in individuals with lumbar spinal stenosis. Spine J 2014;14(9):1936–43.
14. North American Spine Society Evidence Based Clinicl Guidelines for Multidisciplinary Spinal Care. Diagnosis and Treatment of Lumbar Spinal Stenosis. Revised

2011. https://www.spine.org/Documents/ResearchClinicalCare/Guidelines/LumbarStenosis.pdf. Accessed April 24, 2018.
15. North American Spine Society Evidence Based Clinicl Guidelines for Multidisciplinary Spinal Care. Diagnosis and Treatment of Lumbar Degenerative Spondylolisthesis. Revised 2014. Available at: https://www.spine.org/Portals/0/Documents/ResearchClinicalCare/Guidelines/Spondylolisthesis.pdf?ver=2016-04-12-134623-410. Accessed April 24, 2018.
16. Kreiner DS, Shaffer WO, Baisden JL, et al. An evidence-based clinical guideline for the diagnosis and treatment of degenerative lumbar spinal stenosis (update). Spine J 2013;13(7):734–43.
17. De Schepper ET, Overdevest GM, Suri P, et al. Diagnosis of lumbar spinal stenosis. Spine 2013;38(8):E469–81.
18. Katz JN, Harris MB. Clinical practice. Lumbar spinal stenosis. N Engl J Med 2008;358:818–25.
19. Manczak M, Gasik R. Cervical spine instability in the course of rheumatoid arthritis-imaging methods. Reumatologia 2017;55(4):201–7.
20. Andreisek G, Deyo RA, Jarvik JG, et al, LSOS working group. Consensus conference on core radiological parameters to describe lumbar stenosis—an initiative for structured reporting. Eur Radiol 2014;24(12):3224–32.
21. Sigmundsson FG, Kang XP, Jonsson B, et al. Correlation between disability and MRI findings in lumbar spinal stenosis: a prospective study of 109 patients operated on by decompression. Acta Orthop 2011;82:204–10.
22. Geisser ME, Haig AJ, Tong HC, et al. Spinal canal size and clinical symptoms among persons diagnosed with lumbar spinal stenosis. Clin J Pain 2007;23:780–5.
23. Kim HJ, Suh BG, Lee DB, et al. The influence of pain sensitivity on the symptom severity in patients with lumbar spinal stenosis. Pain Physician 2013;16:135–44.
24. Burgstaller JM, Schuffler PJ, Buhmann JM, et al. Is there an association between pain and magnetic resonance imaging parameters in patients with lumbar spinal stenosis? Spine 2016;41(17):E1053–62.
25. Winklhofer S, Held U, Burgstaller JM, et al. Degenerative lumbar spinal canal stenosis: intra- and inter-reader agreement for magnetic resonance imaging parameters. Eur Spine J 2017;26(2):353–61.
26. Dora C, Walchli B, Elfering A, et al. The significance of spinal canal dimensions in discriminating symptomatic from asymptomatic disc herniations. Eur Spine J 2002;11(6):575–81.
27. Ishimoto Y, Yoshimura N, Muraki S, et al. Associations between radiographic lumbar spinal stenosis and clinical symptoms in the general population: the Wakayama Spine Study. Osteoarthritis Cartilage 2013;21(6):783–8.
28. Haig AJ, Tong HC, Yamakawa KS, et al. The sensitivity and specificity of electrodiagnostic testing for the clinical syndrome of lumbar spinal stenosis. Spine (Phila Pa 1976) 2005;30:2667–76.
29. Yagci I, Gundoz OH, Ekinci G, et al. The utility of lumbar paraspinal mapping in the diagnosis of lumbar spinal stenosis. Am J Phys Med Rehabil 2009;88(10):843–51.
30. Kalff R, Ewald C, Waschke A, et al. Degenerative lumbar spinal stenosis in older people. Dtsch Arztebl Int 2013;110(37):613–24.
31. Peng K, Chen L, Peng J, et al. Effects of calcitonin on lumbar spinal stenosis: a systematic review and meta-analysis. Int J Clin Exp Med 2015;8(2):2536–44.
32. Kasimcan O, Kaptan H. Efficacy of gabapentin for radiculopathy caused by lumbar spinal stenosis and lumbar disk hernia. Neurol Med Chir (Tokyo) 2010;50(12):1070–3.

33. Kaye AD, Beuno FR, Katalenich B, et al. The effects of gastroretentive gabapentin (Gralise®) on spinal stenosis patients with radicular pain. Pain Physician 2014; 17(2):169–78.
34. Goren A, Yildiz N, Topuz O, et al. Efficacy of exercise and ultrasound in patients with lumbar spinal stenosis: a prospective randomized controlled trial. Clin Rehabil 2010;24(7):623–31.
35. Lindback Y, Tropp H, Enthoven P, et al. PREPARE: pre-surgery physiotherapy for patients with degenerative lumbar spine disorder: a randomized controlled trial protocol. Spine J 2017 [pii:S1529-9430(17)31217-2].
36. Davis N, Hourigan P, Clarke A. Transforaminal epidural steroid injection in lumbar spinal stenosis: an observational study with two-year follow-up. Br J Neurosurg 2017;31(2):205–8.
37. Chou R, Hashimoto R, Friedly J, et al. Epidural corticosteroid injections for radiculopathy and spinal stenosis: a systematic review and meta-analysis. Ann Intern Med 2015;163(5):373–81.
38. Friedly JL, Comstock BA, Turner JA, et al. A randomized trial of epidural glucocorticoid injections for spinal stenosis. N Engl J Med 2014;371(1):11–21.
39. Cohen SP, Hanling S, Bicket MC, et al. Epidural steroid injections compared with gabapentin for lumbosacral radicular pain: multicenter randomized double blind comparative efficacy study. BMJ 2015;350:h1748.
40. Kim DH, Cho SS, Moon YJ, et al. Factors associated with successful responses to transforaminal balloon adhesiolysis for chronic lumbar foraminal stenosis: retrospective study. Pain Physician 2017;20(6):E841–8.
41. Machado GC, Maher CG, Ferreira PH, et al. Trends, complications, and costs for hospital admission and surgery for lumbar spinal stenosis. Spine 2017;42(22): 1737–43.
42. Carragee EJ. The increasing morbidity of elective spinal stenosis surgery: is it necessary? JAMA 2010;303:1309.
43. Sengupta DK, Herkowitz HN. Degenerative spondylolisthesis: review of current trends and controversies. Spine 2005;30:S71.
44. Bae HW, Rajaee SS, Kanim LE. Nationwide trends in the surgical management of lumbar spinal stenosis. Spine 2013;38(11):916–26.
45. Forsth P, Olafsson G, Carlsson T, et al. A randomized, controlled trial of fusion surgery for lumbar spinal stenosis. N Engl J Med 2016;374(15):1413–23.
46. Deyo RA, Mirza SK, Martin B, et al. Trends, major medical complications, and charges associated with surgery for lumbar spinal stenosis in older adults. JAMA 2010;303:1259.
47. Deyo RA, Martin BI, Ching A, et al. Interspinous spacers compared with decompression or fusion for lumbar stenosis: complications and repeat operations in the Medicare population. Spine 2013;38(10):865–72.
48. Pintauro M, Duffy A, Payman V, et al. Interspinous implants: are the new implants better than the last generation? A review. Curr Rev Musculoskelet Med 2017; 10(2):189–98.
49. Giannadakis C, Solheim O, Jakola AS, et al. Surgery for lumbar spinal stenosis in individuals aged 80 and older: a multicenter observational study. J Am Geriatr Soc 2016;64(10):2011–8.
50. Antoniadis A, Ulrich NH, Schmid S, et al. Decompression surgery for lumbar spinal canal stenosis in octogenarians; a single center experience of 121 consecutive patients. Br J Neurosurg 2017;31(1):67–71.

51. Lagman C, Ugiliweneza B, Boakye M, et al. Spine surgery outcomes in elderly patients versus general adult patients in the United States: a MarketScan analysis. World Neurosurg 2017;103:780–8.
52. Machado GC, Ferreira PH, Yoo RI, et al. Surgical options for lumbar spinal stenosis. Cochrane Database Syst Rev 2016;(11):CD012421.
53. Zaina F, Tomkins-Lane C, Carragee E, et al. Surgical versus non-surgical treatment for lumbar spinal stenosis. Cochrane Database Syst Rev 2016;(1):CD010264.
54. Malmivaara A, Slatis P, Heliovaara M, et al. Surgical or nonoperative treatment for lumbar spinal stenosis? A randomized controlled trial. Spine 2007;32:1–8.
55. Atlas SJ, Keller RB, Wu YA, et al. Long-term outcomes of surgical and nonsurgical management of lumbar spinal stenosis: 8 to 10 year results from the Maine lumbar spine study. Spine 2005;30:936–43.
56. Machado GC, Ferreira ML. No clinically important benefits of surgery over rehabilitation for lumbar spinal stenosis (PEDro synthesis). Br J Sports Med 2017; 51(6):541–2.
57. Delitto A, Piva SR, Moore CG, et al. Surgery versus nonsurgical treatment of lumbar spinal stenosis. Ann Intern Med 2015;163(5):397–8.
58. Benyamin RM, Staats PS, MiDAS Encore I. MILD® is an effective treatment for lumbar spinal stenosis with neurogenic claudication: MiDAS ENCORE randomized controlled trial. Pain Physician 2016;19(4):229–42.

Nonsurgical Management of Osteoarthritis Knee Pain in the Older Adult: An Update

Nora Taylor, MD

KEYWORDS

• Osteoarthritis • Management • Pharmacologic • Nonpharmacologic

KEY POINTS

- Knee osteoarthritis pain relief in older individuals often involves a mix of nonpharmacologic and pharmacologic therapies to achieve maximum benefit.
- Nonpharmacologic therapy in the form of exercise and weight loss, when appropriate, should be emphasized in all elderly patients with knee osteoarthritis to augment pharmacologic therapy.
- Treatment recommendations for older individuals should account for medical comorbidities, patient preference for modality of treatment, and functional status.

INTRODUCTION

The lifetime risk of symptomatic knee osteoarthritis is 44.7% and disproportionately affects elderly patients.[1] With a growing proportion of the population 65 years of age and older, it is estimated that the United States will have 83.7 million older adults by the year 2050.[2] Older adults opting for knee replacement are likely to suffer longer hospital stays and higher risks of both intensive care unit admission and postoperative complications as compared with younger patients.[3] As a result of patient preference and/or medical comorbidities, health care providers need to be prepared to care for and counsel older patients suffering from knee osteoarthritis who are opting to forego total joint replacement. A review of the most recent evidence regarding nonpharmacologic and pharmacologic management techniques for the older adult with knee osteoarthritis is covered here. Successful programs should be designed to meet the needs of the individual and may require multiple modalities to achieve pain reduction and improved function (**Fig. 1**).

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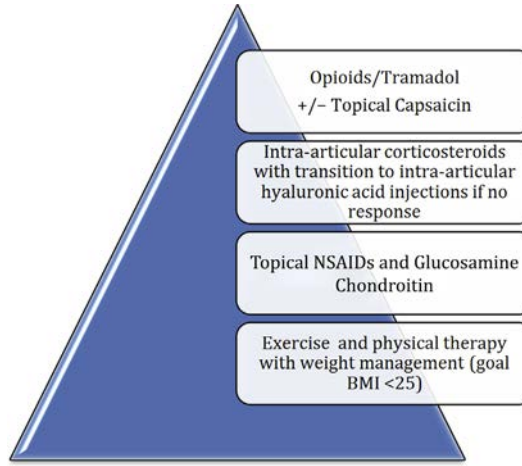

Fig. 1. Recommendations by the author for the treatment of osteoarthritis in the elderly.

NONPHARMACOLOGIC TREATMENT OPTIONS

- Nonpharmacologic management of knee osteoarthritis should focus on exercise and achieving a healthy weight.
- A 7% to 10% weight loss in obese elderly patients with symptomatic knee osteoarthritis should be the initial aim to achieve pain relief.
- Exercise should be tailored to the individual functional level with progressive programs favored.

WEIGHT LOSS

With the rising obesity epidemic in the United States, a large number of elderly patients with knee osteoarthritis will be clinically overweight. It is estimated that one-third of individuals over the age of 60 are obese.[4] Weight loss has been shown to decrease both pain and further cartilage loss. In a study by Gersing and colleagues,[5] a weight loss of greater than 10% over a 48-month time period slowed continued knee cartilage degeneration as measured by T2 images on MRI. Decreased progression of cartilage degeneration was best seen in the medial tibia. Among participants (average age of 62 years) in the study with a greater than 10% weight loss, a statistically significant improvement in pain was measured by the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scales for pain and disability. In a separate study of 192 individuals age 50 or older (average age of 62.5 years) and an average body mass index (BMI) of 37 kg/m^2, a structured weight loss program over 16 weeks determined that 64% of patients had significant pain reduction as measured by the Outcome Measures in Rheumatology (OMERACT)–Osteoarthritis Research Society International (OARSI) Responder Criterion.[6] Clinical improvement related to weight loss was not affected by baseline structural damage, quadriceps strength, or abnormalities in the mechanical axis.

Although weight loss is a frequent recommendation in guidelines for treatment of osteoarthritis, the optimal amount of weight loss to target remains undetermined.[7,8] In an attempt to answer the question, an Australian study involving 1383 individuals with an average age of 64 years and a mean BMI of 34.4 found that a 7.7% weight loss was required to achieve significant pain reduction based on the Knee Injury

and Osteoarthritis Outcome Score.[7] The unique aspect of the study was the search for a specific dose response. A study in *Obesity* evaluated a weight loss and exercise intervention aimed at achieving a 10% reduction in BMI in adults 60 years or older with a BMI $\geq$30. This study noted improved pain relief by WOMAC scoring and significantly improved 6-minute walk test and stair climb with an average 8.7% weight loss.[8] Weight loss in this study occurred over a 6-month time period. When counseling patients on a goal for weight reduction, a 7% to 10% weight loss appears to be sufficient to obtain relief from knee pain and improve function.

EXERCISE

Muscle mass and strength are lost in the natural aging process with a decline in strength appreciable even when muscle mass is maintained.[9] Prevention of obesity and maintaining lean body mass are likely central to ameliorating aging-related musculoskeletal changes.[10] Strength training is one mechanism to achieve this end. Exercise is included in the American College of Rheumatology (ACR), the European League Against Rheumatism (EULAR), and the OARSI recommendations for knee osteoarthritis management.[11–13] EULAR recommendations specify isometric exercise for both legs (to include the quadriceps and proximal hip girdle regions, irrespective of whether one or both knees are involved). Aerobic activity, stretching, and exercise instruction are also recommended.[13] EULAR recommendations favor programs that are "mixed" (involving both aerobic and strength training), that encourage integration of exercise into daily life, and that are progressive in nature.

Providers do not often specify the number of supervised sessions for patients undergoing therapy for knee osteoarthritis, but data from a Cochrane meta-analysis suggest that 12 or more sessions will have the best impact on pain reduction.[14] A *Cochrane Systematic Review* also indicates that patients undergoing land-based exercise therapy will continue to benefit for 2 to 6 months after therapy intervention.[15] Despite these benefits, economic or transportation issues may limit the ability of patients to participate in physical therapy programs. In this case, providers may direct patients to online resources (eg, http://orthoinfo.org/PDFs/Rehab_Knee_6.pdf), which provide patients with home exercises that they can use routinely. Care should be taken to emphasize home safety when following self-management exercise programs so as to avoid falls and injury.

Age and functional limitation should not prevent physicians from considering a trial of physical therapy for knee osteoarthritis. To date, and despite common practice, the available data do not suggest that patients will have a greater benefit from physical therapy if they are provided with an intra-articular glucocorticoid injection before therapy.[16]

Pharmacologic Intervention: Key Points

- Topical therapies are preferred over oral therapies for osteoarthritis pain relief in the elderly to avoid medication interactions and side effects.
- Topical nonsteroidal anti-inflammatory medications (NSAIDs) and pharmaceutical grade glucosamine and chondroitin provide modest pain relief for individuals with symptomatic knee osteoarthritis along with a favorable side-effect profile.
- Intra-articular corticosteroids can provide limited duration pain improvement.
- Intra-articular hyaluronic acid (IA-HA) injections may provide a longer duration of pain relief but are less efficacious in short-term pain relief as compared with intra-articular corticosteroids. The optimal preparation of injectable hyaluronic acid to achieve pain relief remains unclear.

- Opioids and mixed mechanism μ-receptor agonists should be reserved for cases of knee osteoarthritis that have failed standard interventions.

TOPICAL THERAPIES

Topical Nonsteroidal Anti-Inflammatory Agents

Topical preparations of NSAIDs for the treatment of osteoarthritis range from over-the-counter pain balms to prescription medications. In the United States, topical diclofenac is available in a gel, solution, and patch.[17] The goal of topical preparations of NSAIDs is to achieve local anti-inflammatory effect with minimal systemic absorption. Efficacy and safety of topical NSAIDs in the treatment of osteoarthritis, collectively in trials, were evaluated in a recent review. Equal efficacy of topical NSAIDs as compared with oral NSAIDs in the treatment of knee osteoarthritis was found at 1 year.[18] The oral group experienced more respiratory adverse events and a greater increase in serum creatinine. Change of therapy in the oral NSAID group due to negative side effects was more common than in the topical NSAID group. No major adverse events, defined as death or hospitalization, were noted between the oral and topical NSAID groups. The overall low risk of adverse effects from oral NSAIDs in the trial was attributed to the strict exclusion criteria for the study. Therefore, it remains difficult to determine the relevance of these findings to an elderly population. The ACR specifically addressed adults over the age of 75 in their pharmacologic recommendations for the treatment of knee osteoarthritis by strongly recommending topical NSAID preparations over oral NSAIDs given the risk factors for oral NSAID use for adults in this age category.[12]

Although warnings regarding gastrointestinal, cardiac, and renal adverse effects are listed on package inserts for topical NSAID preparations, these side effects are only rarely reported in follow-up studies. In a report using pooled data from 3 studies of topical diclofenac for treating knee osteoarthritis, the risk of gastrointestinal events was equivalent when comparing the topical NSAID with placebo intervention groups for both patients aged 25 to 64 and those older than 65.[19] However, a significant improvement in the WOMAC pain scale for knee osteoarthritis was not observed until after week 12 in patients over the age of 65, perhaps related to more severe knee osteoarthritis in this group.

Given the safety profile of topical NSAIDs compared with oral NSAIDs in the elderly population, topical NSAIDs are an excellent initial intervention for the pharmacologic treatment of knee osteoarthritis. Because patients using the topical NSAIDs (as opposed to oral NSAIDs) report a higher level of pain at the 3-month assessment time, this may indicate that in order to achieve similar long-term effects as with oral NSAIDs, greater patience with the continued use of topical NSAIDs may be required. Topical NSAIDs are directly addressed in the OARSI guidelines for patients with isolated knee osteoarthritis and comorbidities.[13] The committee that generated these guidelines considered the quality of evidence for the endorsed use of topical NSAIDs to be “good.”

Capsaicin

Capsaicin, found in the root of hot peppers, is used in topical preparations for the relief of osteoarthritis pain and is available both over the counter and by prescription. Topical capsaicin acts through depletion of type-C nociceptive nerve fibers, thereby impairing neuronal release of substance P and ultimately modulating the local sensory response. Pain signals are dampened with recurrent capsaicin application. For knee osteoarthritis, topical capsaicin is applied in a thin layer 4 times daily. Local skin

irritation occurs commonly, and care must be taken so as not to accidentally touch or splatter the mucous membranes or the eyes.

In a review of randomized controlled trials of topical capsaicin (of which 3 of the 5 reviews specified knee osteoarthritis), Laslett and Jones[20] noted only a moderate change in the visual analogue scale (VAS) pain scale over a 4-week time period. No systemic toxicity was noted, but topical irritation was recorded in 35% to 100% of participants. The 2013 OARSI guidelines recommend the use of topical capsaicin in knee osteoarthritis patients without comorbidities but made no assertion about benefit in patients possessing comorbidities.[13] In contrast, the 2012 ACR guidelines did not recommend the use of topical capsaicin given the lack of high-quality evidence supporting its use.[12] In a 2013 *Cochrane Review* of topical herbal therapies for osteoarthritis, capsaicin (Capsicum) gel was not noted to be more effective than placebo.[21] With a high likelihood of skin irritation, and with the requirement for frequent application, along with insufficient evidence of efficacy, the pragmatic use of capsaicin treatment might be reserved for the situation of an older patient seeking to forestall a trial of opioid therapy.

Intra-Articular Corticosteroid Injections

Intra-articular corticosteroid injections are commonly used by physicians in the care of osteoarthritis knee pain. Intra-articular corticosteroid injections are an in-office procedure with significant appeal for both physician and patient given the excellent safety profile with minimal systemic side effects.[22] However, pain relief may be variable in degree and modest in duration. The EULAR, OARSI, and ACR guidelines all include recommendations for the use of intra-articular corticosteroids for the treatment of knee osteoarthritis pain. Contraindications to injection include infection at the injection site, sepsis, or a preexisting knee replacement.

Based on a *Cochrane Review* of intra-articular corticosteroids for knee osteoarthritis that pooled 27 studies with 1767 total participants, intra-articular glucocorticoids improved pain relief by a difference of 1.0 cm on a 10-cm VAS as compared with sham injections.[23] The therapeutic effect of injections does not have a prolonged duration. A small to moderate benefit compared with placebo was observed 4 to 6 weeks after injection; a small effect was observed at 13 weeks, and no difference was noted at 26 weeks. Patients may require repeat injections for pain relief, although the safe interval between injections and optimal preparation of steroid has yet to be established.[24] There are no predictors of response to intra-articular steroid injections based on available data to date, making it difficult to counsel patients prognostically. Data for the use of intra-articular corticosteroids are stronger than that of IA-HA injections with regards to short-term pain relief; however, with time, IA-HA may be more efficacious for pain relief.[25] Most studies evaluate patients in the sixth decade. No study specifically addresses the benefit of intra-articular steroids in the very elderly.

In October 2017, FX006, an extended release formulation of triamcinolone acetonide, trademarked as Zilretta, was released for the treatment of knee osteoarthritis. Although trials showed benefit in mean pain scores compared with placebo (saline injection), there was no statistical difference in average daily pain intensity scores when comparing FX006 to immediate release triamcinolone. Of the 424 patients who received FX006 at the 32-mg dose in clinical studies, 143 patients were aged 65 or older. No differences in adverse effects were noted between younger and older patients. Based on available data (as cited in US Food and Drug Administration prescribing guide downloaded from Flexion Therapeutics Web site accessed February 8, 2018), it does not appear that use of FX006 offers a substantial benefit over shorter-acting preparations of intra-articular glucocorticoids.

Performing intra-articular glucocorticoid injections in older adults may require special advance preparation and positional aids in order to work around patient limitations. Patients who are unable to move to the examination table or are unable to extend their knee may have injections via an anterior infrapatellar lateral or medial approach. Utilization of the infrapatellar approach with the knee flexed to 90° and aiming toward the midline is a well-tolerated and popular technique among rheumatologists. The anterior-lateral infrapatellar approach may have improved accuracy data as compared with the anterior-infrapatellar medial approach in this situation.[26]

If knee anatomy is distorted by advanced osteoarthritis or body habitus, image-guided injection should be considered. As many as one of every 5 nonvisualized knee injections does not enter the intra-articular space (a number that may be higher for inexperienced physicians or in cases of patients with challenging anatomy). Bedside ultrasound-guided injection is an appealing option. Ultrasound-guided injections provide better short-term outcomes and less injection site complications as compared with blinded injections. However, long-term outcomes appear to be similar between image-guided and palpation-guided injections.[27]

Intra-Articular Hyaluronic Acid Injections

Conflicting data exist for the use of IA-HA injections for the treatment of knee osteoarthritis. First approved in 1997, viscosupplementation was thought to improve shock absorption and provide improved lubrication and pain relief in the knee. Different preparations of IA-HAs are marketed, and the frequency of injection ranges from single-dose injection (eg, Synvisc-One) to multidose injections given as a series once weekly over several weeks (eg, Euflexxa). Guidelines from the ACR make no specific recommendations regarding the use of IA-HA injections beyond noting that their use may be appropriate for individuals 75 years of age and older and who cannot take oral NSAIDs.[12] OARSI guidelines report “uncertain” benefit in the use of IA-HA for knee osteoarthritis.[13] More recently, the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) published recommendations for the use of IA-HA injections in patients who have an inadequate response to NSAID use.[28] Given the risks to older patients from chronic NSAID use, IA-HA injections may be more appropriate. A multicenter trial has demonstrated equal short-term efficacy between these 2 therapies.[29]

Meta-analyses of the use of IA-HA injections for osteoarthritis pain suffer from confounding due to heterogeneity in the preparations and a lack of double-blind placebo controlled trials. Pain relief is variable among the different IA-HA formulations. Intra-articular corticosteroids appear to have better short-term effect on pain control, whereas IA-HA injections may have improved pain relief at the 8-week mark.[27] Potential residual benefit is reported up to 24 weeks in some studies. The reported effect size in a 2011 meta-analysis of IA-HA injections was 0.46 (>0.20 is considered clinically relevant), which was greater than that for acetaminophen and NSAIDs.[30] The optimal preparation of IA-HA agent is not known, but there is evidence that patients may derive greater benefit from higher-molecular-weight IA-HAs.[31] Berenbaum and colleagues[32] in a 2012 study found a higher proportion of OMERACT-OARSI responders with high-molecular-weight IA-HA (73%) versus the intermediate-molecular-weight IA-HA preparations (58%) at the 6-month mark. Despite these findings, there remains insufficient evidence to support the use of one IA-HA preparation over another.

A systematic review of the effectiveness of IA-HA injections on physical functioning for those patients with severe degenerative osteoarthritis and an average age of 65 or older revealed a small but statistically significant improvement with few serious

adverse effects.[33] However, when only double-blinded, sham-controlled trials are considered, no therapeutic difference is observed between IA-HA injections and placebo. Therefore, although the benefit to older adults appears less than certain, IA-HA remains a viable option owing in large part to its relative safety profile.[34]

ORAL THERAPIES

Nonsteroidal Anti-Inflammatory Drugs

NSAIDs have strong data to support their use for pain relief in osteoarthritis. Unfortunately, the deleterious effects to kidneys, as well as to the cardiovascular and gastrointestinal systems, make them a riskier choice in older adults.[35,36] Cyclooxygenase-2 inhibitors (COX-2), such as Celecoxib, possess reduced gastrointestinal toxicity but remain a concern with regards to cardiovascular risk.[37] Given the risk profile of both NSAIDs and COX-2 inhibitors, the author favors sporadic use with careful monitoring in otherwise healthy patients between 65 and 75 years of age and avoids their use altogether in patients 75 and older.

Acetaminophen

Acetaminophen is widely used in the management of osteoarthritis of the knee. Its use is recommended by the ACR for the management of osteoarthritis, and it is considered "appropriate" for use in patients without relevant comorbidities (OARSI treatment guidelines).[12,13] Although acetaminophen is relatively safe for younger individuals without comorbidities, it may confer a greater risk in frail older adults and also may not provide as substantial pain relief as once hoped.[35] In a *Cochrane Review* in 2006 evaluating the efficacy of acetaminophen in treating hip and knee osteoarthritis, the number needed to treat with acetaminophen to achieve a 5% pain reduction ranged from 4 to 16 individuals.[38] In the situation of liver impairment, acetaminophen is contraindicated. If acetaminophen is to be used for pain control, doses up to 4 g daily (and continuously) are often required in order to achieve a modest pain relief benefit. Therefore, care must be taken to evaluate the medication list of all patients using high-dose acetaminophen in order to ensure that underappreciated ingestion of other acetaminophen-containing medications does not place individuals at increased risk for toxicity.

Glucosamine and Chondroitin

The use of glucosamine and chondroitin has undergone significant scrutiny over the past decade. The Glucosamine/Chondroitin Arthritis Intervention Trial found no evidence for effective pain reduction in knee osteoarthritis; however, subgroup analysis noted a trend toward pain relief in patients with moderate to severe knee pain.[39] Previous evaluations of glucosamine sulfate have found that only the crystalline glucosamine sulfate formulations were associated with significant pain and structural benefits. Chondroitin may also provide a modest benefit with regards to pain relief. In a recent *Cochrane Review* of the effects of chondroitin on osteoarthritis pain, it was found that patients experience an average 8-point (scale 0–100) reduction in pain using chondroitin while enduring fewer side effects than placebo.[40] Although this review looked primarily at patients with knee osteoarthritis, some of the included trials examined patients with hip and hand osteoarthritis as well.

Recent guidelines for the management of symptomatic knee osteoarthritis published by the ESCEO suggest use of prescription dose (1500 mg) of patented crystalline glucosamine sulfate as a first-line therapy.[28] Use of patented crystalline glucosamine sulfate has similar efficacy to NSAIDs, and possibly better efficacy

than that reported for paracetamol or acetaminophen preparations.[41] Chondroitin, either used in combination with glucosamine or alone, was also recommended as a first-line treatment. Some yet to be replicated studies report a reduction in joint space narrowing with the use of combination pharmaceutical grade glucosamine and chondroitin with fewer adverse events compared with placebo.[42,43] The safety profile of glucosamine and chondroitin makes them attractive agents in elderly patients. However, difficulty in obtaining prescription grade glucosamine and/or chondroitin may limit their use.

Tramadol and Other Opioids

Use of opioid analgesics in the treatment of knee osteoarthritis in the elderly may pose challenges owing to tolerability, increased fall risk, withdrawal, and constipation. Elderly patients may experience age-related decline in clearance of opiates from their system in addition to a risk of polypharmacy reducing efficacy or leading to adverse outcomes.[44] Geriatric Society Guidelines address these concerns in the 2009 report on pharmacologic management of persistent pain in older adults.[45] Opioid management of knee osteoarthritis pain should be considered on a trial basis initially and with strict follow-up for management and monitoring. The increase of opioid misuse and accidental deaths has led to evolving steps by the US Health and Human Services Secretary and Centers for Disease Control and Prevention to address opioid-prescribing practices with a focus on utilization of the minimally effective dose.[46,47] Specific reference is made to utilization of a multimodal approach to pain management when opioids are used.

Tramadol and tapentadol, analgesics with activity on the μ-opioid receptor as well as norepinephrine and serotonin reuptake inhibition, are generally reserved for refractory knee pain in patients who have failed other pain management modalities. Tramadol and tapentadol should be considered when all alternate options have been exhausted and the patient remains hampered by daily knee pain.[48] Short- and long-acting preparations are available to allow practitioners to develop optimized dosing schedules for their patients. Data suggest that the benefit of opioids in the treatment of osteoarthritis pain is similar to that of NSAIDs. The effect of mixed mechanism μ-opioid agonists and opiates in the treatment of knee osteoarthritis is equivalent as per the OARSI.[13] For this reason, many practitioners favor the use of tramadol when opioid-agonist therapy is deemed necessary.

If opioids are not effective in achieving a substantial decrease in osteoarthritis knee pain, then these agents should be discontinued as soon as possible to minimize tolerance, dependence, and potential for adverse side effects. In a 2014 *Cochrane Review*, oral and transdermal opioids for the treatment of knee and hip osteoarthritis improved both function and pain scores. An average 0.7-mm improvement in pain on a 10-mm VAS was noted with the use of opioids compared with placebo.[49] This modest benefit in pain relief was associated with a 22% opioid side-effect rate. A recent review and comparison of 27 randomized controlled trials comparing NSAIDs, tramadol, and opioids revealed similar rates of pain relief among the medications, suggesting that providers should choose the safest option for their particular patient when discussing oral therapies.[50,51]

Recently, published data on a model of cost-effectiveness of opioid use in knee osteoarthritis revealed that use of tramadol and tramadol with oxycodone increased cost and decreased quality-adjusted life-years (QALYs) as compared with opioid sparing (NSAIDs, physical therapy, and intra-articular steroid injections followed by total knee replacement if ineffective). Although opioid use delayed time until total knee replacement, both opioid treatment strategies increased cost and decreased QALYs

as compared with opioid-sparing strategies. In patients without substantial comorbidities that would prevent any future potential for knee replacement, this data should be considered when discussing possible opioid use with patients.

SUMMARY

The nonsurgical care of the elderly patient with symptomatic knee osteoarthritis should consist of combination treatment with nonpharmacologic and pharmacologic modalities. Goals should be aimed at pain reduction and improved function while minimizing potential negative side effects, in particular those associated with long-term oral opioid use. Progressive exercise programs and weight loss remain pillars of nonpharmacologic therapy. Topical NSAIDs and pharmaceutical grade glucosamine and/or chondroitin can provide modest pain relief with minimal potential adverse effects. Intra-articular injections of corticosteroids and IA-HA injections are generally safe and well tolerated by elderly patients and should be used to augment pain relief.

REFERENCES

1. Murphy L, Schwartz TA, Helmick CG, et al. Lifetime risk of symptomatic knee osteoarthritis. Arthritis Rheum 2008;59(9):1207–13.
2. Ortman JV, V. 2014. Available at: https://www.census.gov/prod/2014pubs/p25-1140.pdf.
3. Fang M, Noiseux N, Linson E, et al. The effect of advancing age on total joint replacement outcomes. Geriatr Orthop Surg Rehabil 2015;6(3):173–9.
4. Porter Starr KN, Bales CW. Excessive body weight in older adults. Clin Geriatr Med 2015;31(3):311–26.
5. Gersing AS, Solka M, Joseph GB, et al. Progression of cartilage degeneration and clinical symptoms in obese and overweight individuals is dependent on the amount of weight loss: 48-month data from the Osteoarthritis Initiative. Osteoarthritis Cartilage 2016;24(7):1126–34.
6. Gudbergsen H, Boesen M, Lohmander LS, et al. Weight loss is effective for symptomatic relief in obese subjects with knee osteoarthritis independently of joint damage severity assessed by high-field MRI and radiography. Osteoarthritis Cartilage 2012;20(6):495–502.
7. Atukorala I, Makovey J, Lawler L, et al. Is there a dose response relationship between weight loss and symptom improvement in persons with knee osteoarthritis? Arthritis Care Res (Hoboken) 2016;68(8):1106–14.
8. Miller GD, Nicklas BJ, Davis C, et al. Intensive weight loss program improves physical function in older obese adults with knee osteoarthritis. Obesity (Silver Spring) 2006;14(7):1219–30.
9. Goodpaster BH, Park SW, Harris TB, et al. The loss of skeletal muscle strength, mass, and quality in older adults: the health, aging and body composition study. J Gerontol A Biol Sci Med Sci 2006;61(10):1059–64.
10. Fielding RA. The role of progressive resistance training and nutrition in the preservation of lean body mass in the elderly. J Am Coll Nutr 1995;14(6):587–94.
11. Fernandes L, Hagen KB, Bijlsma JW, et al. EULAR recommendations for the nonpharmacological core management of hip and knee osteoarthritis. Ann Rheum Dis 2013;72(7):1125–35.
12. Hochberg MC, Altman RD, April KT, et al. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. Arthritis Care Res (Hoboken) 2012;64(4):465–74.

13. McAlindon TE, Bannuru RR, Sullivan MC, et al. OARSI guidelines for the non-surgical management of knee osteoarthritis. Osteoarthritis Cartilage 2014;22(3):363–88.
14. Fransen M, McConnell S. Land-based exercise for osteoarthritis of the knee: a metaanalysis of randomized controlled trials. J Rheumatol 2009;36(6):1109–17.
15. Fransen M, McConnell S, Harmer AR, et al. Exercise for osteoarthritis of the knee: a Cochrane systematic review. Br J Sports Med 2015;49(24):1554–7.
16. Henriksen M, Christensen R, Klokker L, et al. Evaluation of the benefit of corticosteroid injection before exercise therapy in patients with osteoarthritis of the knee: a randomized clinical trial. JAMA Intern Med 2015;175(6):923–30.
17. McPherson ML, Cimino NM. Topical NSAID formulations. Pain Med 2013;14(suppl 1):S35–9.
18. Underwood M, Ashby D, Cross P, et al. Advice to use topical or oral ibuprofen for chronic knee pain in older people: randomised controlled trial and patient preference study. BMJ 2008;336(7636):138–42.
19. Baraf HS, Gloth FM, Barthel HR, et al. Safety and efficacy of topical diclofenac sodium gel for knee osteoarthritis in elderly and younger patients: pooled data from three randomized, double-blind, parallel-group, placebo-controlled, multicentre trials. Drugs Aging 2011;28(1):27–40.
20. Laslett LL, Jones G. Capsaicin for osteoarthritis pain. Prog Drug Res 2014;68:277–91.
21. Cameron M, Chrubasik S. Topical herbal therapies for treating osteoarthritis. Cochrane Database Syst Rev 2013;(5):CD010538.
22. Cardone DA, Tallia AF. Joint and soft tissue injection. Am Fam Physician 2002;66(2):283–8.
23. Juni P, Hari R, Rutjes AW, et al. Intra-articular corticosteroid for knee osteoarthritis. Cochrane Database Syst Rev 2015;(10):CD005328.
24. Douglas RJ. Corticosteroid injection into the osteoarthritic knee: drug selection, dose, and injection frequency. Int J Clin Pract 2012;66(7):699–704.
25. Bannuru RR, Natov NS, Obadan IE, et al. Therapeutic trajectory of hyaluronic acid versus corticosteroids in the treatment of knee osteoarthritis: a systematic review and meta-analysis. Arthritis Rheum 2009;61(12):1704–11.
26. Douglas RJ. Aspiration and injection of the knee joint: approach portal. Knee Surg Relat Res 2014;26(1):1–6.
27. Maricar N, Parkes MJ, Callaghan MJ, et al. Where and how to inject the knee–a systematic review. Semin Arthritis Rheum 2013;43(2):195–203.
28. Bruyere O, Cooper C, Pelletier JP, et al. A consensus statement on the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) algorithm for the management of knee osteoarthritis-from evidence-based medicine to the real-life setting. Semin Arthritis Rheum 2016;45(4 suppl):S3–11.
29. Ishijima M, Nakamura T, Shimizu K, et al. Intra-articular hyaluronic acid injection versus oral non-steroidal anti-inflammatory drug for the treatment of knee osteoarthritis: a multi-center, randomized, open-label, non-inferiority trial. Arthritis Res Ther 2014;16(1):R18.
30. Bannuru RR, Natov NS, Dasi UR, et al. Therapeutic trajectory following intra-articular hyaluronic acid injection in knee osteoarthritis–meta-analysis. Osteoarthritis Cartilage 2011;19(6):611–9.
31. Berenbaum F, Grifka J, Cazzaniga S, et al. A randomised, double-blind, controlled trial comparing two intra-articular hyaluronic acid preparations

differing by their molecular weight in symptomatic knee osteoarthritis. Ann Rheum Dis 2012;71(9):1454–60.
32. Kotevoglu N, Iyibozkurt PC, Hiz O, et al. A prospective randomised controlled clinical trial comparing the efficacy of different molecular weight hyaluronan solutions in the treatment of knee osteoarthritis. Rheumatol Int 2006;26(4):325–30.
33. Newberry SJ. AHRQ technology assessments, in systematic review for effectiveness of hyaluronic acid in the treatment of severe degenerative joint disease (DJD) of the knee. Rockville (MD): Agency for Healthcare Research and Quality (US); 2015.
34. Abate M, Pulcini D, Di Iorio A, et al. Viscosupplementation with intra-articular hyaluronic acid for treatment of osteoarthritis in the elderly. Curr Pharm Des 2010; 16(6):631–40.
35. American Geriatrics Society Panel on the Pharmacological Management of Persistent Pain in Older Persons. Pharmacological management of persistent pain in older persons. Pain Med 2009;10(6):1062–83.
36. Amer M, Bead VR, Bathon J, et al. Use of nonsteroidal anti-inflammatory drugs in patients with cardiovascular disease: a cautionary tale. Cardiol Rev 2010;18(4): 204–12.
37. Scarpignato C, Lanas A, Blandizzi C, et al. Safe prescribing of non-steroidal anti-inflammatory drugs in patients with osteoarthritis–an expert consensus addressing benefits as well as gastrointestinal and cardiovascular risks. BMC Med 2015; 13:55.
38. Towheed TE, Maxwell L, Judd MG, et al. Acetaminophen for osteoarthritis. Cochrane Database Syst Rev 2006;(1):CD004257.
39. Clegg DO, Reda DJ, Harris CL, et al. Glucosamine, chondroitin sulfate, and the two in combination for painful knee osteoarthritis. N Engl J Med 2006;354(8): 795–808.
40. Singh JA, Noorbaloochi S, MacDonald R, et al. Chondroitin for osteoarthritis. Cochrane Database Syst Rev 2015;(1):CD005614.
41. Herrero-Beaumont G, Ivorra JA, Del Carmen Trabado M, et al. Glucosamine sulfate in the treatment of knee osteoarthritis symptoms: a randomized, double-blind, placebo-controlled study using acetaminophen as a side comparator. Arthritis Rheum 2007;56(2):555–67.
42. Hochberg M, Chevalier X, Henrotin Y, et al. Symptom and structure modification in osteoarthritis with pharmaceutical-grade chondroitin sulfate: what's the evidence? Curr Med Res Opin 2013;29(3):259–67.
43. Bruyere O, Reginster JY. Glucosamine and chondroitin sulfate as therapeutic agents for knee and hip osteoarthritis. Drugs Aging 2007;24(7):573–80.
44. O'Neil CK, Hanlon JT, Marcum ZA. Adverse effects of analgesics commonly used by older adults with osteoarthritis: focus on non-opioid and opioid analgesics. Am J Geriatr Pharmacother 2012;10(6):331–42.
45. American Geriatrics Society Panel on Pharmacological Management of Persistent Pain in Older Persons. Pharmacological management of persistent pain in older persons. J Am Geriatr Soc 2009;57(8):1331–46.
46. McCarthy M. Opioids should be last resort to treat chronic pain, says draft CDC guideline. BMJ 2015;351:h6905.
47. Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain–United States, 2016. JAMA 2016;315(15):1624–45.
48. Santos J, Alarcão J, Fareleira F, et al. Tapentadol for chronic musculoskeletal pain in adults. Cochrane Database Syst Rev 2015;(5):CD009923.

49. da Costa BR, Nüesch E, Kasteler R, et al. Oral or transdermal opioids for osteoarthritis of the knee or hip. Cochrane Database Syst Rev 2014;(9):CD003115.
50. Smith SR, Deshpande BR, Collins JE, et al. Comparative pain reduction of oral non-steroidal anti-inflammatory drugs and opioids for knee osteoarthritis: systematic analytic review. Osteoarthritis Cartilage 2016;24(6):962–72.
51. Smith SR, Katz JN, Collins JE, et al. Cost-effectiveness of tramadol and oxycodone in the treatment of knee osteoarthritis. Arthritis Care Res (Hoboken) 2017; 69(2):234–42.