Cardiovascular disease and bone health in aging female rheumatic disease populations: A review

**Marven G Cabling, Vaneet K Sandhu, Christina D Downey
and Karina D Torralba** iD

Abstract

Rheumatic diseases cover a wide spectrum of conditions, including primary and secondary degenerative joint diseases and autoimmune inflammatory rheumatic diseases. The risks of cardiovascular disease and osteoporosis and resultant fractures in aging female rheumatic disease populations, especially those with autoimmune rheumatic diseases, are increased. Changes in the immune system in aging populations need to be considered especially among patients with autoimmune rheumatic diseases. Immunosenescence is closely aligned to reduced adaptive immunity and increased non-specific innate immunity leading to chronic inflammation of inflammaging. The effective use of disease-modifying antirheumatic drugs to control autoimmune rheumatic diseases may also mitigate factors leading to cardiovascular disease and osteoporosis. Rheumatic diseases, which largely manifest as arthritis, predispose patients to premature joint degeneration and poor bone health and therefore have a higher risk of developing end-stage arthritis requiring joint arthroplasties sooner or more often than other patients without rheumatic disease.

Keywords

arthroplasty, glucocorticoids, immunosenescence, inflammaging, osteoporosis, rheumatoid arthritis, systemic lupus erythematosus

Introduction

Most developed nations are seeing a graying of their populations. In the United States, adults over the age of 65 will outnumber children for the first time, making up 21% of the population by the year 2030. In addition, the number of older adults is expected to nearly double to 95 million in 2060.[1] Recent medical advances have led to improved life expectancy from 68 years in 1950 to 77 in 2020.[2] However with an aging population, we now see a higher prevalence of infections and chronic and degenerative diseases, including cardiovascular disease (CVD), Alzheimer's disease, arthritis, and malignancy.

Rheumatic diseases cover a wide spectrum of conditions, including primary and secondary degenerative joint diseases, and autoimmune inflammatory rheumatic diseases. We report herein the current practice in rheumatology and review selected relevant literature exploring the changes that occur in the immune system with aging, their potential impact on aging female rheumatic disease populations, and the inherent risks for the development of CVD and osteoporosis in this population. We also wish to briefly highlight the prevalence and impact of joint arthroplasties on aging female rheumatic disease populations.

Immunosenescence and inflammaging

The aging of the immune system, called "immunosenescence," leads to a progressive decline in the body's response

Division of Rheumatology, Department of Medicine, Loma Linda University School of Medicine, Loma Linda, CA, USA

Corresponding author:
Karina D Torralba, Division of Rheumatology, Department of Medicine, Loma Linda University School of Medicine, 11234 Anderson Street, MC-1516 - E, Loma Linda, CA 92354, USA.
Email: Ktorralba@llu.edu

to stressors and pathogens.[3] One of the main drivers of this process is the remodeling of lymphoid organs, specifically the involution of the thymus as one ages. This leads to decreased T lymphocyte function and ineffective central tolerance where there is a decrease in regulatory and naïve T cells.[4,5] This immune system reorganization contributes to a chronic low-grade sterile inflammation seen in older adults called "inflammaging."[6] With this process, there is an increase in acute phase reactants such as the C-reactive protein (CRP), and cytokines including interleukins 6 (IL-6) and 1 (IL-1) and tumor necrosis factor alpha (TNF-α) in the elderly.[7] This pro-inflammatory state is attributed to the somatic cellular senescence-associated secretory phenotype (SASP) and chronic innate immune activation. However, self-reactive T lymphocytes seem to be a primary contributor to inflammaging as well, making the process autoimmune or self-reactive in origin.[5,8] Simply put, immunosenescence is linked to reduced adaptive immunity while there is an increase in non-specific innate immunity, leading to inflammaging. This complex interplay predisposes the aging individual to development of autoimmune disease, malignancies, infections, and decreased responsiveness to vaccinations,[4,8,9] translating to an overall increased morbidity and mortality in the elderly.[10]

Inflammaging and immunosenescence are implicated in the development of autoimmune rheumatic diseases (ARD) such as rheumatoid arthritis (RA). In general, with aging, there is a decline in the generation of naive and regulatory T cells which results in a compensatory proliferation of mature T cells in the periphery. Over time, the continuous replication of mature T cells leads to exhaustion and eventual production of its senescent phenotype. This process is accelerated in patients with RA, where senescent T cells are found much higher compared to the normal population (Figure 1).[11] Coupled with a decreased central tolerance, this likely contributes to the higher incidence of RA in adults >60 years old. The prevalence of RA is also higher at 2.03%–2.34%, compared to 0.5%–1% in younger adults.[12]

It should be cautioned, however, that while autoimmunity increases in the elderly this does not necessarily translate to an increase in autoimmune disease in this population.[13] Various autoimmune diseases present differently in older adults than in their younger counterparts. For example, in RA a subset of patients would develop elderly onset RA (EORA) at age >60. The phenotype of EORA contrasts from younger-onset RA with more balanced gender distribution, and an increased involvement of larger joints especially the shoulder girdle, resembling polymyalgia rheumatica (PMR). Also, there is a tendency for EORA to present more acutely with higher disease activity and increased systemic symptoms compared to younger counterparts.[14]

In systemic lupus erythematosus (SLE), the majority of patients are young, reproductive age females. However, about 12%–18% will have a delayed onset of SLE after
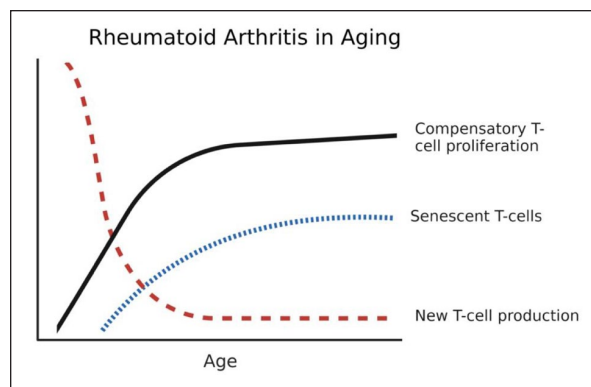

Figure 1. Immunosenescence in rheumatoid arthritis. As the immune system ages, T-cell production from the thymus decreases and this process is accelerated in patients with rheumatoid arthritis. With the decrease of thymic T-cell population, a compensatory and excessive proliferation of peripheral T cells ensues causing them to eventually be senescent. Senescent T cells have an autoreactive and pro-inflammatory phenotype which contribute to the inflammatory features of the disease. Adapted from Weyand and Goronzy 2002. Image created BioRender.com (Weyand and Goronzy[11]).

age 50–65.[15] Females are still predominantly affected but the female to male ratio in late-onset SLE is decreased from 9:1 to 5-7:1.[16] Late-onset SLE is considered to be more indolent compared to younger onset, especially with lower prevalence of anti-dsDNA and hypocomplementemia.[15,16] There is also less involvement of skin, mucus membranes, joints, kidneys, and hematological abnormalities, but more frequent incidence of serositis, depression and thrombotic events when compared to their younger counterparts.[17]

As one ages, there is an accumulation of comorbidities making it common for patients to have multiple disease processes at the same time, a condition called "multimorbidity" (Figure 2). In RA, the average patient has 1.6 additional conditions and this is expected to increase with age and disease activity.[18] These competing and interrelated diseases increase the complexity of how we care for older patients. Along with RA-related comorbidities, older adults are already at risk for cognitive impairment, depression, falls, urinary incontinence, and malnutrition. These are found to be more prevalent in patients with rheumatic diseases. These lead to increased adverse outcomes including accumulation of added morbidity, nursing home admission and mortality.[19] It is thus imperative for the clinician to recognize the changes and unique challenges that the older adult patients face in order to adequately care for them.

CVD in aging rheumatic disease populations

In 2019, 35% of total deaths in women were due to CVD.[20] In countries with a low socio-demographic index (measured
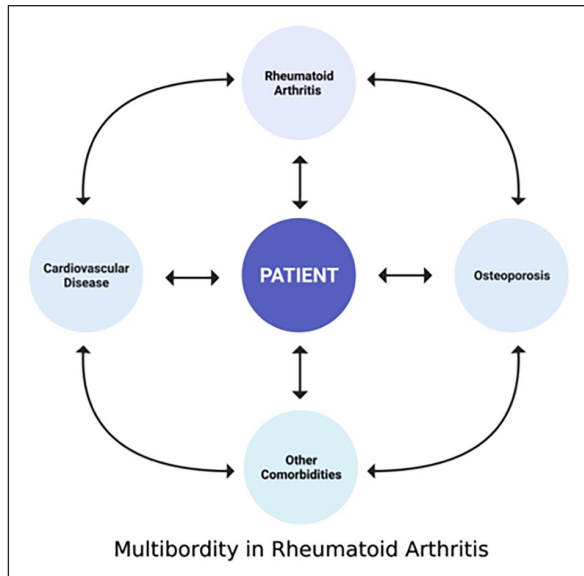
Figure 2. Rheumatoid arthritis (RA) is a systemic disease, and most patients have multiple other comorbid illnesses. Using the concept of multimorbidity, the patient is the center of the treatment paradigm where there is no index disease. Each comorbidity is given adequate importance, taking note of the interaction of each coexisting condition, and treating with the goal of patient improvement and quality of life. Adapted from Radner et al.[18] Created with BioRender.com.

by a composite of income per capita, educational attainment, and fertility rates), CVD mortality is greater in women than men.[21] Even in developed countries like the United States and Canada; however, the decline in cardiovascular (CV) mortality has slowed with a more recent uptick in acute myocardial infarctions in younger women.[22,23] Overall, CVD in women is underdiagnosed with an underrepresentation in clinical trials thereby limiting progress in diagnosis and management in this population.[24] The disparity of CVD treatment utilization in women compared to men is likely related to differences in clinical manifestations of CVD and comorbidities.[25–27] Such disparities are further compounded by an aging population of individuals with rheumatic disease, which largely impact women greater than men.[28]

Menopause, the heart, and autoimmunity

The risk for CVD increases with interrupted ovarian function, as in menopause, whereby the cardioprotective benefits of estrogen are reduced or lost.[29] Specifically, the declining estrogen levels trigger an increase in low-density lipoprotein (LDL) and total cholesterol in addition to the impact on receptors in the vasculature.[30] An earlier age at menopause is linked to a greater risk of CVD and all-cause mortality.[31] One hypothesis for this is that CVD risk is increased by mechanisms beyond estrogen depletion

alone, and that menopause before age 45 years may be a red herring for CVD-related events.[32]

In ARDs, CVD is a major cause for morbidity and mortality and occurs due to underlying disease activity, medication use, and additional risk factors.[33] When evaluating the burden of mortality associated with autoimmune diseases grouped together, they rank among the top 10 causes of death in women under 75 years of age.[34,35] Furthermore, in evaluating menopause, autoimmunity, and heart disease, one must consider the impact of rheumatic disease treatments on the reproductive system. In SLE, for example, premature ovarian failure is described in more than 60% of patients with a history of treatment with cyclophosphamide,[36] a medication known for its adverse effects of teratogenicity and ovarian failure.

Pathogenesis

Atherosclerosis is a chronic disease that presents itself clinically as a myocardial infarction. What starts as endothelial dysfunction results in an atheromatous plaque formed by foamy macrophages in the arterial intima, where collagen, elastin, and proteoglycan are deposited.[37] Premature atherosclerosis is a result of chronic inflammation as seen in individuals with ARD. The impact of ARDs on traditional CV risk factors (e.g. smoking, hypertension) as well as the use of potentially cardio-toxic medications (e.g. non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids (GCs), certain disease-modifying antirheumatic drugs (DMARDs) adds layers of complexity to the pathophysiology of CVD in ARDs.[38] Autoantibody formation in ARDs like SLE have also been implicated in premature atherosclerosis as demonstrated by the presence of IgG-continuing immune complex deposits in premature atherosclerotic lesions.[39]

While obstructive coronary artery disease (CAD) is conventionally a disease of older males, cardiac syndrome X has been ascribed to myocardial ischemia occurring because of microvascular dysfunction (MVD), typically presenting in women with chest pain and myocardial ischemia without angiographic evidence of coronary stenosis.[40] MVD is largely underdiagnosed, impacts women aged 45–65 years, and is associated with major adverse CV events.[41,42]

Cardiovascular manifestations

It is important to remember that vascular disease in ARDs is typically described as premature atherosclerosis not otherwise related to traditional CV risk factors.

Valvular disease, typically of the mitral valve, is common in patients with ARD, seen in at least 30% of patients with RA and SLE, though largely asymptomatic.[43,44] Such valvular abnormalities noted in ARD are to be considered in combination with underlying risks for valvular disease, including senescence.

Table 1. Cardiovascular disease risk factors in females with autoimmune rheumatic diseases.

Family history of premature atherosclerotic CVD (females <65 years)
Primary hypercholesterolemia
Metabolic syndrome
Chronic kidney disease
Chronic inflammatory diseases (e.g. Psoriasis, RA, SLE, etc.)
Premature menopause (before age 40 years)
History of preeclampsia
High risk race/ethnicity (e.g. South Asian ancestry)
Lipid profile (hypertriglyceridemia)
Elevated C-reactive protein
Elevated apolipoprotein
Elevated lipoprotein A
Ankle brachial index <0.9 (peripheral vascular disease)

Source: Adapted from Grundy et al.[53]
CVD: cardiovascular disease; RA: rheumatoid arthritis; SLE: systemic lupus erythematosus.

Manifesting as sudden cardiac death (SCD), atrial or ventricular arrythmias, or atrioventricular block, electrical abnormalities are not infrequent in ARD. The main cause of SCD in RA is related to acute coronary syndrome and resulting ventricular arrhythmias.[45] In SLE, sinus tachycardia, atrial fibrillation, and ectopic atrial beats are associated with flares and myocarditis.[46] Antibodies to Ro/SSA are associated with sinus bradycardia and prolonged QT interval.[45] From small vessel vasculitis to fibrosis of the conduction nodes and bundle branches, ARDs can impact the electrophysiology of the heart in ways that can otherwise be improperly categorized as "age-related" or related to other comorbidities.

While pulmonary hypertension (PH) can complicate many ARDs, systemic sclerosis (SSc) is the foremost ARD that presents with PH.[47] Additional etiologies include thromboembolic PH seen in antiphospholipid syndrome or PH from veno-occlusive disease in SSc. PH is only second to interstitial lung disease in being the leading cause of death in SSc, thereby emphasizing the importance of prompt diagnosis and management.[48] Early diagnosis is limited by coexisting symptoms of ARD that may limit an optimal clinical evaluation. For example, fatigue and reduced exercise tolerance may be discounted as a manifestation of one's age or underlying rheumatic disease.[49] Recognizing risk factors for PH and being proactive in evaluating for PH can mitigate some of these misinterpretations.

Myocardial disease due to ARDs typically presents in the form of congestive heart failure and is believed to occur from a chronic pro-inflammatory state. In SLE and SSc, most cases are asymptomatic.[43,50]

Pericardial disease is a frequent manifestation in SLE, SSc, and RA. Clinically, this may present as pericarditis with fever and pleuritic chest pain, or with more clinically significant pericardial effusion with shortness of breath and hypotension.[43]

Cardiovascular risks

Senescence of various components of the CV system implicates biological age as a critical determinant of onset and progression of CVD.[51] Hypertension, which affects more than 60% of adults aged 45–75 years in the United States, is another key player in the development of CVD.[52]

The 2018 AHA Guidelines on cholesterol management describe CVD risk-enhancing factors to include a family history of premature atherosclerotic CVD, persistently elevated LDL levels, metabolic syndrome, chronic kidney disease, a history of premature menopause (<40 years) or preeclampsia, high-risk ethnic groups like South Asians, persistently elevated triglycerides, elevated apolipoprotein B, and chronic inflammatory diseases like RA, psoriasis, and other ARDs (Table 1).[53] The Framingham Offspring Study demonstrated that women with SLE <45 years of age are 50 times more likely to have a myocardial infarction compared to non-SLE patients of the same age.[54] In RA, the risk of CVD mortality is 50% greater than the general population.[55] Traditional risk factors such as hyperlipidemia and hypertension are generally more prevalent in SLE patients, related either to disease state such as lupus nephritis or medications such as GCs. In addition, antiphospholipid antibodies, seen in 30%–50% of patients with SLE, may affect the lipid profile through lipid peroxidation, which furthers endothelial dysfunction.[56,57]

Historically, GCs were used universally to treat ARD. More recently, however, many studies have demonstrated complications from long-term use and high doses of GCs, including but not limited to an increase in blood glucose, triglycerides, and blood pressure, all independent risk factors for CVD.[58] Similar associations of NSAIDs and other immune modulatory therapy with hypertension and CVD have been noted.

Lipid levels, though implicated in CVD, can be normal in half of all myocardial infarctions.[59] While lipid deposition

within arterial vasculature is typical of atherogenesis, inflammation is an independent risk factor for CVD.[60] Serum high-sensitivity CRP (hs-CRP) and IL-6, both markers for inflammation, bear serologic risk for CV events.[61,62] An elevated CRP is also associated with a greater likelihood of myocardial infarction in patients with angina in addition to death from CVD in smokers with other atherosclerotic risk factors.[63,64] Cigarette smoking is independently associated with a higher CRP.[65]

In SLE, older age at disease onset, longer duration of SLE, higher damage score, elevated serum LDL and homocysteine, and greater duration of treatment with GCs are associated with an increased risk for CVD.[66] The risk for PH in SSc includes the limited form of SSc, the presence of centromere antibody, telangiectasias, increased duration of illness, older age, and elevated uric acid levels. The risk for cardiopulmonary hospitalization in scleroderma is associated with dyspnea, pericardial effusion, and a diffusing capacity of carbon monoxide (DLCO) of less than 50%.[67] In RA, where the risk for a myocardial infarction is two-fold greater than controls, a reduced risk of CV disease is noted in those individuals treated with DMARDs such as TNF-α inhibitors and methotrexate.[66,68]

CVD risk models, including the Framingham risk score, Systematic Coronary Risk Evaluation (SCORE), and the Reynolds Risk Score underestimate CVD risk in RA and other rheumatic diseases.[69] Because of this, non-invasive cardiovascular risk stratification can be considered through coronary artery calcification score and carotid ultrasonography to identify those patients considered "moderate risk" concerning the SCORE or modified EULAR score.[70–72] The European guidelines on CV disease prevention in clinical practice recommend multiplying the risk SCORE by 1.5 to ascertain CV risk in ARD.[73] In SLE, Petri et al.[74] established that the risk for CVD-related events varied based on SLE-related risk factors like SELENA-SLEDAI score, the presence of low C3 and lupus anticoagulant in addition to traditional risk factors. Urowitz et al.[75] proposed a CVD risk score by multiplying the Framingham risk score by two.

Diagnosis and management of CVD

The diagnosis of CVD in ARD can be made through traditional imaging and interventional modalities. Carotid ultrasonography may uncover subclinical atherosclerosis through carotid intima-media thickening.[76] Similarly, echocardiography, coronary computed tomography, and positron emission tomography are valuable tools aiding in the diagnosis and risk stratification of patients with ARD and suspected CVD.[77] Cardiac magnetic resonance imaging can also be used as a non-invasive modality to identify coronary MVD in patients with unremarkable conventional CVD evaluation.[78]

PH evaluation is largely clinical on initial screening. When PH is suspected, or in the case of all patients with SSc and SSc-related diseases, annual screening echocardiography is warranted.[79] The DETECT algorithm incorporates the use of lung volume studies (forced vital capacity/diffusion capacity of the lung for carbon monoxide, FVC/DLCO ratio), positive centromere antibody, current or prior telangiectasias, serum uric acid and N-terminal-pro hormone B-type natriuretic peptide levels, and a right axis deviation on electrocardiography to assess risk of PH in patients with SSc.[80]

The subclinical nature of CVD in women with ARD, combined with increased morbidity and mortality, calls for early diagnosis and prompt treatment. The association of CVD onset and progression with disease activity stresses the importance of concomitantly controlling signs and symptoms of ARD. Longitudinal registry data of patients with RA in the United States has demonstrated that reduced disease activity is associated with fewer CV events.[81] In more experimental phases, treatment with anti-inflammatory agents such as the IL-1β receptor antagonist canakinumab, and colchicine improves CVD outcomes in various cohorts.[66–68]

The presence of ARD plays a significant role in accelerated senescence, including CVD. Comprehensive risk stratification, assessment, and management of these additional CVD risk factors should be standard of care in women with ARD. Collaborative care efforts between cardiology, rheumatology, and primary care, are critical to closing the gap in CV care in women with ARD.

Bone health in aging rheumatic disease populations

Inflammation related to ARDs largely predisposes to the development of osteoporosis (OSP). When compounded with female sex and elderly age, the risk of OSP in aging females with ARDs becomes much higher (Table 2).

Rheumatoid arthritis. RA is highly associated with OSP, affecting as many as 50% of all patients, with the risk for men and premenopausal women being double that of those without RA in age matched controls.[82] Periarticular osteopenia, a decrease in both cortical and trabecular bone, increased cortical porosity and lower volumetric bone mineral density (BMD) are all hallmarks of RA (Figure 3).[83] The mechanisms for this are many such as contributions by TNF-α and IL-6 release indirectly leading to receptor activation of nuclear factor kappa-B ligand (RANKL) activation which in turn activates osteoclast formation and activation while simultaneously decreasing osteoblastogenesis. The Wnt signaling pathway is also inhibited in RA patients via increased levels of Dickkopf-related protein 1 (Dkk-1).[84] This explains why higher RA disease activity is associated with higher degree of pathologic bone loss. Further, RA patients with anti-cyclic citrullinated peptide antibodies have an even higher incidence

Table 2. Assessment of osteoporosis in patients with autoimmune rheumatic diseases.

Factors contributing to osteoporosis:
   Age >50
   Female gender, menopause
   Low body mass index
   Prior history of fracture
   Family history of osteoporosis
   Smoking; excessive alcohol intake
   Nutrition (e.g. insufficient vitamin D and calcium intake)
   Inactivity or lack of physical activity
   Sarcopenia (muscle loss)
   High disease activity of underlying ARD
   Use of glucocorticoids

Diagnosis of osteoporosis is made in the presence of any of the following:
1. Low T-score ($\leqslant -2.5$) on dual-energy X-ray absorptiometry (DXA). However, most patients who sustain a fracture have osteopenia, with a T-score of -1 to -2.5 on DXA
2. Fragility fracture or a fracture resulting from a ground level fall
3. A 10-year probability of $\geqslant 3\%$ for any major osteoporotic, or $\geqslant 20\%$ for hip fractures, using the Fracture Risk Assessment (FRAX) tool (available on https://www.sheffield.ac.uk/FRAX)

The assessment of osteoporosis includes a global clinical evaluation of the patient's history, risk factors, physical examination, basic laboratory assessment, and evaluation using the FRAX tool. An understanding of caveats related to the use of DXA and FRAX is imperative. Majority of patients who fracture have osteopenia on DXA.

ARD: autoimmune rheumatic diseases.

Figure 3. Plain radiograph of a patient with long-standing rheumatoid arthritis (RA). The image shows extensive erosive and destructive changes on all the metacarpophalangeal (MCP) joints on both hands. These resulted in ulnar deviation of the digits. Also note the significantly decreased bone density around the MCPs and carpal/wrist joints (periarticular osteopenia), which indicates chronic inflammatory activity from this patient's years of untreated disease. RA is an independent risk factor for osteoporosis and affects as much as 50% of RA patients.

of OSP, which is thought to be mediated by IL-6-dependent osteoclast activation.[83]

While uncontrolled RA is one contributor to poor bone health in this disease, decrease in physical activity and resultant bone loading and development of sarcopenia further exacerbates the risk of OSP and subsequent fractures. Further, patients with periarticular erosions are also at risk for trabecular bone loss which is another reason

poor disease control is associated with an increased risk for OSP.[85]

The role of GC-associated bone loss cannot be divorced from a discussion about OSP in RA patients. GCs directly encourage apoptosis of osteoblasts and an increase in Dkk-1 and sclerostin via the Wnt pathway in a time and dose dependent manner leading to loss of trabecular bone strength. Further, high doses of GCs shift production of bone stem cells from osteoblasts to adipocytes. GCs increase the osteoclast life cycle via the RANKL pathway. Finally, GCs inhibit absorption of calcium in the intestine and renal tubules.[86] Both RA and GCs cause decrease in muscle mass (rheumatoid cachexia and sarcopenia) which leads to a decrease in bone loading, further worsening the strength of the bones in the RA patient. Poor strength is a risk factor for poor balance and increased risk of falling, leading to an increased risk for fragility fractures.

On the other hand, GCs are a mainstay of terminating acute flares of RA, which decrease disease activity leading to an improvement in bone health. The interplay between RA disease activity, GC use, and bone health is complicated. Nevertheless, short courses of low dose GCs in patients with early and active RA appear to be safe and not have a significant negative effect on BMD. This is likely due to the established advantage of GCs in controlling disease activity.[87] It then makes sense that treating the underlying inflammation will improve or at least stabilize the BMD of patients with RA. Indeed, several studies have shown positive evidence supporting this. The use of TNF-α inhibitors was found to be associated with decreased vertebral fractures in a U.S.-wide observational cohort.[88]

Similarly, favorable outcomes in BMD were found for other biologics such as abatacept and tocilizumab, with no significant difference in the risk of fractures between these drugs and TNF-α inhibitors.[89] Overall, treating the underlying RA is beneficial in preventing or even improvement bone loss in this population.

Systemic lupus erythematosus. A relationship between low BMD, resultant fractures, and SLE has been established in many populations worldwide.[90] An estimated prevalence of 20%–26% of vertebral fractures exists in SLE patients, with a 4.7-fold increase in risk of fracture in female SLE patients versus healthy controls.[91] In male patients with SLE, the incidence rate ratio for developing OSP is 5.35.[92]

Risk factors unique to patients with SLE for bone loss include low levels of C4, absence of anti-Smith autoantibodies, presence of anti-Ro/SSA, presence of lupus anticoagulant, use of anticoagulants, use of anti-epileptic medications, FOK-I vitamin D receptor FF or Ff genotype and low serum levels of dehydroepiandrosterone. As in RA, the likelihood of low BMD increases with decreasing body weight, increased disease activity, and use of GCs, particularly in doses >7.5 mg daily or for prolonged periods. Lupus nephritis and subsequent aberrations in parathyroid hormone, calcium, and vitamin D are further risk factors for low BMD in patients with SLE.[92]

Spondyloarthropathies. The spondyloarthropathies including psoriatic arthritis and ankylosing spondylitis are characterized by increased bony proliferation, rather than loss of BMD as is seen in RA. However, low BMD is found in patients early in the disease process. Reduction in physical activity, spinal mobility, ankylosis and decreased functional capacity place patients with axial spondylarthritis at substantial risk for vertebral fractures after very minimal trauma. In fact, the risk of vertebral fractures in this patient group is higher than that found in patients with RA (odds ratio of 7.1 vs 2.7).[93] Fractures occur more frequently in the cervical spine than in patients with primary osteoporosis, leading to a higher risk of neurologic compromise. Thankfully, the risk of fractures elsewhere such as the wrist or the hip is not raised to the same degree as that of vertebral fractures.[94]

Fusion of the cervical spine and decreased range of motion at the hips and lumbar spine increase the risk for falls in this population (Figure 4). These factors also make accurate assessment of fracture risk difficult by dual-energy X-ray absorptiometry or bone densitometry and trabecular bone score, and therefore, the use of fracture risk evaluations such as FRAX® (Fracture Risk Assessment Tool) scoring may help more accurately identify patients at risk for fragility fractures. High disease activity, longer disease duration, low weight, low body mass index, and male gender were positively associated with OSP.[95] As with other chronic inflammatory diseases, reduction in
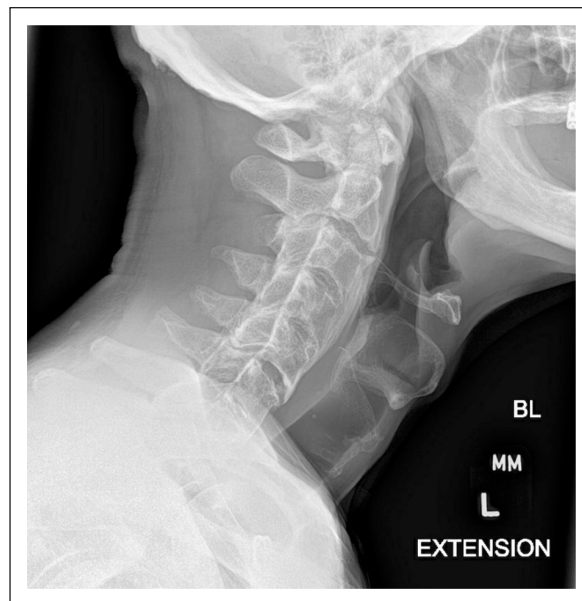

Figure 4. Plain radiograph of the cervical spine in a patient with ankylosing spondylitis (AS). The image shows significant anterior and posterior osseous fusion (ankylosis) of the C3-5 vertebrae. Despite the proliferative bone changes, patients with spondyloarthropathies, including AS, are more prone to cervical spine fractures than patients with primary osteoporosis. The resulting decreased range of motion of the spine also increases the risk for falls and thus fractures in this population.

disease activity with biologic agents reduces the likelihood of loss of BMD in this patient population.[93]

Vasculitis. Even prior to treatment with GCs, there is an increased prevalence of osteopenia in patients with antineutrophil cytoplasmic antibody or ANCA-associated vasculitis, suggesting a mechanism driven by a chronic inflammatory state.[96] However, due to the organ and life-threatening nature of the diseases, vasculitis patients tend to stay on GC therapy at some level for long periods with standard of care being at least 52 weeks, even when other treatment modalities are used concurrently.[97] Furthermore, relapses are common in vasculitides, particularly large vessel vasculitis, for which GCs are largely used.[98] In patients with Giant Cell Arteritis and PMR, the frequency of OSP has been found to be up to 85% and the incidence of fractures in this group was found to be 11%–14%.[99]

Inflammatory myopathy. BMD is decreased in patients with inflammatory myopathies through mechanisms similar to what is described above in relation to chronic inflammation. Demineralization due to immobility contributes to poor bone health as well. Like the vasculitides, GC therapy is a cornerstone of treatment for these conditions and is another driver of poor skeletal health in this patient group.

Arthroplasties in the aging female population

It is impossible to talk about bone health in aging female rheumatic disease populations without delving into the prevalence and impact of joint arthroplasties.

Arthritis often leads to disability and poor quality of life. In the United States, it is the most common cause of disability, affecting approximately 54.4 million (22.7%) adults. It is projected that this number will rise to 78.4 million by the year 2040.[100] As arthritis progresses, it may lead to joint destruction causing end-stage arthritis, severe pain, and functional disability needing surgical joint replacement. Arthritis and arthralgia are major manifestations of rheumatic musculoskeletal diseases, whether or not autoimmune or inflammatory in nature. The use of joint arthroplasties may mitigate bone loss in these populations, as they improve physical functionality including the ability to ambulate in these patients. The most common indication for joint replacement surgery is osteoarthritis (OA). However, patients with ARDs are disproportionately at risk for requiring joint replacements than the general population. This is likely due to the underlying inflammatory pathology that brings about more rapid destruction of the joint compared to OA. Those with psoriatic arthritis and RA are two and four times, respectively, more likely to undergo joint replacement surgery compared to non-RA patients.[101,102] Similarly, patients with SLE are at higher risk and tend to be younger and female compared to patients with OA needing arthroplasty perhaps due to the increased risk for osteonecrosis in this population.[103]

The overall prevalence of total hip arthroplasties (THA) and total knee arthroplasties (TKA) in the United States is 0.83% and 1.52%, respectively.[104] Projections on the overall use of these surgeries are predicted to increase by 284% and 401% by year 2040.[105] The increase in the aging population and the obesity epidemic has been linked to an increase in OA cases, thus the rise in joint replacements.[106] Of note, the prevalence of arthritis is higher in females than males (26% vs 19.1%), if adjusted for age.[107] Consequently, the rate of joint replacements is higher in older women.[104] Furthermore, female gender was found to be an independent risk factor for readmission, reoperation, and wound infection after total hip replacement, while male gender was an independent risk for the same outcomes but for total knee replacement surgery. In either case, females tend to require more hospital length of stay than males.[108] Frail patients who receive joint replacements tend to be female and sicker which leads to higher mortality and perioperative complications following primary and revision THA.[109,110]

Overall, the outcomes of joint replacement surgery are good and are associated with significant improvement in quality of life.[111] This is also observed even in those with rheumatic musculoskeletal diseases. Interestingly, patients with RA are not at higher risk of acute surgical site infection after TKA compared to those with OA.[112] Similarly, SLE was not found to be an independent risk factor for poor short-term pain or function after either hip or knee arthroplasty.[113] Over the past 20 years with the increasing use of DMARDs especially the biologic agents, the proportion of patients with inflammatory arthritis who needed to undergo joint replacement surgeries has decreased.[114] This contrasts with an increase in joint replacements in patients with OA over time.[115]

Conclusion

The risks of CVD and osteoporosis and resultant fractures in aging female rheumatic disease populations, especially those with ARD, are increased. Changes in the immune system in aging populations need to be considered especially among patients with ARD. Immunosenescence is closely aligned to reduced adaptive immunity and increased non-specific innate immunity leading to chronic inflammation of inflammaging. The effective use of DMARDs to control ARD, may also mitigate factors leading to CVD and osteoporosis. Rheumatic diseases which largely manifest with arthritis predispose patients to premature joint degeneration and poor bone health and therefore have a higher risk of developing end-stage arthritis and the need for joint arthroplasties sooner or more often than other patients without rheumatic disease.

Declarations

Author contribution(s)

Marven G Cabling: Conceptualization; Data curation; Writing—original draft; Writing—review & editing.
Vaneet K Sandhu: Conceptualization; Data curation; Writing—original draft; Writing—review & editing.
Christina D Downey: Conceptualization; Data curation; Writing—original draft; Writing—review & editing.
Karina D Torralba: Conceptualization; Data curation; Writing—original draft; Writing—review & editing.

ORCID iD

Karina D Torralba (iD) https://orcid.org/0000-0003-4741-1213

References

1. Vespa J, Medina L and Armstrong D. Demographic turning points for the United States: population projections for 2020 to 2060: population estimates and projections: current population reports, https://www.census.gov/content/dam/Census/library/publications/2020/demo/p25-1144.pdf (2020, accessed 16 July 2022).
2. Murphy S, Kochanek K, Xu J, et al. Mortality in the United States, 2020: NCHS data brief, https://www.cdc.gov/nchs/products/databriefs/db427.htm#Key_finding (2021, accessed 16 July 2022).
3. Aw D, Silva AB and Palmer DB. Immunosenescence: emerging challenges for an ageing population. *Immunology* 2007; 120(4): 435–446.
4. Lian J, Yue Y, Yu W, et al. Immunosenescence: a key player in cancer development. *J Hematol Oncol* 2020; 13: 151.
5. Thomas R, Wang W and Su DM. Contributions of age-related thymic involution to immunosenescence and inflammaging. *Immun Ageing* 2020; 17: 2.
6. Franceschi C, Bonafè M, Valensin S, et al. Inflamm-aging. An evolutionary perspective on immunosenescence. *Ann N Y Acad Sci* 2000; 908: 244–254.
7. Michaud M, Balardy L, Moulis G, et al. Proinflammatory cytokines, aging, and age-related diseases. *J Am Med Dir Assoc* 2013; 14(12): 877–882.
8. Nikolich-Žugich J. The twilight of immunity: emerging concepts in aging of the immune system. *Nat Immunol* 2018; 19: 10–19.
9. Santos-Moreno P, Burgos-Angulo G, Martinez-Ceballos MA, et al. Inflammaging as a link between autoimmunity and cardiovascular disease: the case of rheumatoid arthritis. *RMD Open* 2021; 7(1): e001470.
10. Franceschi C, Garagnani P, Parini P, et al. Inflammaging: a new immune-metabolic viewpoint for age-related diseases. *Nat Rev Endocrinol* 2018; 14(10): 576–590.
11. Weyand CM and Goronzy JJ. Premature immunosenescence in rheumatoid arthritis. *J Rheumatol* 2002; 29: 1141–1146.
12. Rasch EK, Hirsch R, Paulose-Ram R, et al. Prevalence of rheumatoid arthritis in persons 60 years of age and older in the United States: effect of different methods of case classification. *Arthritis Rheum* 2003; 48(4): 917–926.
13. Watad A, Bragazzi NL, Adawi M, et al. Autoimmunity in the elderly: insights from basic science and clinics—a mini-review. *Gerontology* 2017; 63(6): 515–523.
14. Bajocchi G, La Corte R, Locaputo A, et al. Elderly onset rheumatoid arthritis: clinical aspects. *Clin Exp Rheumatol* 2000; 18(4 Suppl. 20): S49–S50.
15. Rovenský J and Tuchynová A. Systemic lupus erythematosus in the elderly. *Autoimmun Rev* 2008; 7: 235–239.
16. Formiga F, Moga I, Pac M, et al. Mild presentation of systemic lupus erythematosus in elderly patients assessed by SLEDAI. SLE Disease Activity Index. *Lupus* 1999; 8(6): 462–465.
17. Frutos AR, Holgado S, Bergé AS, et al. Late-onset versus early-onset systemic lupus: characteristics and outcome in a national multicentre register (RELESSER). *Rheumatology* 2021; 60: 1793–1803.
18. Radner H, Yoshida K, Smolen JS, et al. Multimorbidity and rheumatic conditions-enhancing the concept of comorbidity. *Nat Rev Rheumatol* 2014; 10(4): 252–256.
19. Van Onna M and Boonen A. Challenges in the management of older patients with inflammatory rheumatic diseases. *Nat Rev Rheumatol* 2022; 18(6): 326–334.
20. Vogel B, Acevedo M, Appelman Y, et al. The Lancet women and cardiovascular disease Commission: reducing the global burden by 2030. *Lancet* 2021; 397: 10292.
21. Roth GA, Johnson C, Abajobir A, et al. Global, regional, and national burden of cardiovascular diseases for 10 causes, 1990 to 2015. *J Am Coll Cardiol* 2017; 70: 1–25.
22. Lopez AD and Adair T. Is the long-term decline in cardiovascular-disease mortality in high-income countries over? Evidence from national vital statistics. *Int J Epidemiol* 2019; 48: 1815–1823.
23. Arora S, Stouffer GA, Kucharska-Newton AM, et al. Twenty year trends and sex differences in young adults hospitalized with acute myocardial infarction. *Circulation* 2019; 139: 1047–1056.
24. Legato MJ, Johnson PA and Manson JE. Consideration of sex differences in medicine to improve health care and patient outcomes. *JAMA* 2016; 316: 1865–1866.
25. Redfors B, Angeras O, Ramunddal T, et al. Trends in gender differences in cardiac care and outcome after acute myocardial infarction in Western Sweden: a report from the Swedish web system for enhancement of evidence-based care in heart disease evaluated according to recommended therapies (SWEDEHEART). *J Am Heart Assoc* 2015; 4(7): e001995.
26. Nanna MG, Wang TY, Xiang Q, et al. Sex differences in the use of statins in community practice. *Circ Cardiovasc Qual Outcomes* 2019; 12(8): e005562.
27. Udell JA, Fonarow GC, Maddox TM, et al. Sustained sex-based treatment differences in acute coronary syndrome care: insights from the American Heart Association Get With The Guidelines Coronary Artery Disease Registry. *Clin Cardiol* 2018; 41(6): 758–768.
28. Fairweather D, Frisancho-Kiss S and Rose NR. Sex differences in autoimmune disease from a pathological perspective. *Am J Pathol* 2008; 173(3): 600–609.
29. Mendelsohn ME and Karas RH. The protective effects of estrogen on the cardiovascular system. *N Engl J Med* 1999; 340: 1801–1811.
30. Sammaritano LR. Menopause in patients with autoimmune diseases. *Autoimmun Rev* 2012; 11(6–7): A430–A436.
31. Muka T, Oliver-Williams C, Kunutsor S, et al. Association of age at onset of menopause and time since onset of menopause with cardiovascular outcomes, intermediate vascular traits, and all-cause mortality: a systematic review and meta-analysis. *JAMA Cardiol* 2016; 1: 767–776.

32. Bertone-Johnson ER and Manson JE. Early menopause and subsequent cardiovascular disease. *Menopause* 2015; 22(1): 1–3.

33. Wasko MC. Comorbid conditions in patients with rheumatic diseases: an update. *Curr Opin Rheumatol* 2004; 16(2): 109–113.

34. Walsh SJ and Rau LM. Autoimmune diseases: a leading cause of death among young and middle-aged women in the United States. *Am J Public Health* 2000; 90(9): 1463–1466.

35. Thomas SL, Griffiths C, Smeeth L, et al. Burden of mortality associated with autoimmune diseases among females in the United Kingdom. *Am J Public Health* 2010; 100(11): 2279–2287.

36. Tsaliki M, Koelsch KA, Chambers A, et al. Ovarian antibodies among SLE women with premature menopause after cyclophosphamide. *Int J Rheum Dis* 2021; 24(1): 120–124.

37. Munro JM and Cotran RS. The pathogenesis of atherosclerosis: atherogenesis and inflammation. *Lab Invest* 1988; 58(3): 249–261.

38. Van Onna M and Boonen A. The challenging interplay between rheumatoid arthritis, ageing and comorbidities. *BMC Musculoskelet Disord* 2016; 17: 184.

39. Ansari A, Larson PH and Bates HD. Vascular manifestations of systemic lupus erythematosus. *Angiology* 1986; 37: 423–432.

40. Kemp HG Jr. Left ventricular function in patients with the anginal syndrome and normal coronary arteriograms. *Am J Cardiol* 1973; 32: 375–376.

41. Maas A. Maintaining cardiovascular health: an approach specific to women. *Maturitas* 2019; 124: 68–71.

42. Bairey Merz CN, Pepine CJ, Walsh MN, et al. Ischemia and no obstructive coronary artery disease (INOCA): developing evidence-based therapies and research agenda for the next decade. *Circulation* 2017; 135: 1075–1092.

43. Owlia MB, Mostafavi Pour Manshadi SM and Naderi N. Cardiac manifestations of rheumatological conditions: a narrative review. *ISRN Rheumatol* 2012; 2012: 463620.

44. Prasad M, Hermann J, Gabriel SE, et al. Cardio-rheumatology: cardiac involvement in systemic rheumatic disease. *Nat Rev Cardiol* 2015; 12(3): 168–176.

45. Seferovic PM, Ristic AD, Maksimovic R, et al. Cardiac arrhythmias and conduction disturbances in autoimmune rheumatic diseases. *Rheumatology* 2006; 45(Suppl. 4): iv39–iv42.

46. Teixeira RA, Borba EF, Pedrosa A, et al. Evidence for cardiac safety and antiarrhythmic potential of chloroquine in systemic lupus erythematosus. *Europace* 2014; 16(6): 887–892.

47. Vonk MC, Vandecasteele E and van Dijk AP. Pulmonary hypertension in connective tissue diseases, new evidence and challenges. *Eur J Clin Invest* 2021; 51(4): e13453.

48. Tyndall AJ, Bannert B, Vonk M, et al. Causes and risk factors for death in systemic sclerosis: a study from the EULAR Scleroderma Trials and Research (EUSTAR) database. *Ann Rheum Dis* 2010; 69(10): 1809–1815.

49. Mularek-Kubzdela T, Ciurzynski M, Kowal Bielecka O, et al. An expert opinion of the Polish Cardiac Society Working Group on Pulmonary Circulation and the Polish Society for Rheumatology on the diagnosis and treatment of pulmonary hypertension in patients with connective tissue disease. *Kardiol Pol* 2021; 79(7–8): 917–929.

50. Kahan A, Coghlan G and McLaughlin V. Cardiac complications of systemic sclerosis. *Rheumatology* 2009; 48(Suppl. 3): iii45–iii48.

51. Fulop T, Witkowski JM, Pawelec G, et al. On the immunological theory of aging. *Interdiscip Top Gerontol* 2014; 39: 163176.

52. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation* 2018; 138: e426–e483.

53. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation* 2019; 139: e1046–e1081.

54. McMahon M, Hahn BH and Skaggs BJ. Systemic lupus erythematosus and cardiovascular disease: prediction and potential for therapeutic intervention. *Expert Rev Clin Immunol* 2011; 7(2): 227–241.

55. 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: 1690–1697.

56. Love PE and Santoro SA. Antiphospholipid antibodies: anticardiolipin and the lupus anticoagulant in systemic lupus erythematosus (SLE) and in non-SLE disorders. Prevalence and clinical significance. *Ann Intern Med* 1990; 112: 682–698.

57. Petri M. Epidemiology of the antiphospholipid antibody syndrome. *J Autoimmun* 2000; 15(2): 145–151.

58. Rho YH, Oeser A, Chung CP, et al. Drugs used in the treatment of rheumatoid arthritis: relationship between current use and cardiovascular risk factors. *Arch Drug Inf* 2009; 2(2): 34–40.

59. Braunwald E. Shattuck lecture--cardiovascular medicine at the turn of the millennium: triumphs, concerns, and opportunities. *N Engl J Med* 1997; 337: 1360–1369.

60. Ross R. Atherosclerosis--an inflammatory disease. *N Engl J Med* 1999; 340: 115–126.

61. Ridker PM, Cushman M, Stampfer MJ, et al. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. *N Engl J Med* 1997; 336: 973–979.

62. Ridker PM, Hennekens CH, Buring JE, et al. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. *N Engl J Med* 2000; 342: 836–843.

63. Pietila K, Harmoinen A, Hermens W, et al. Serum C-reactive protein and infarct size in myocardial infarct patients with a closed versus an open infarct-related coronary artery after thrombolytic therapy. *Eur Heart J* 1993; 14(7): 915–919.

64. Thompson SG, Kienast J, Pyke SD, et al. Hemostatic factors and the risk of myocardial infarction or sudden death in patients with angina pectoris. European Concerted

Action on Thrombosis and Disabilities Angina Pectoris Study Group. *N Engl J Med* 1995; 332: 635–641.

65. Das I. Raised C-reactive protein levels in serum from smokers. *Clin Chim Acta* 1985; 153: 9–13.

66. Roman MJ and Salmon JE. Cardiovascular manifestations of rheumatologic diseases. *Circulation* 2007; 116: 2346–2355.

67. Hsu VM, Chung L, Hummers LK, et al. Risk factors for mortality and cardiopulmonary hospitalization in systemic sclerosis patients at risk for pulmonary hypertension, in the PHAROS registry. *J Rheumatol* 2019; 46(2): 176–183.

68. Marks JL and Edwards CJ. Protective effect of methotrexate in patients with rheumatoid arthritis and cardiovascular comorbidity. *Ther Adv Musculoskelet Dis* 2012; 4(3): 149–157.

69. 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): 668–674.

70. Corrales A, Parra JA, Gonzalez- Juanatey C, et al. Cardiovascular risk stratification in rheumatic diseases: carotid ultrasound is more sensitive than Coronary Artery Calcification Score to detect subclinical atherosclerosis in patients with rheumatoid arthritis. *Ann Rheum Dis* 2013; 72(11): 1764–1770.

71. Corrales A, Gonzalez-Juanatey C, Peiro ME, et al. Carotid ultrasound is useful for the cardiovascular risk stratification of patients with rheumatoid arthritis: results of a population-based study. *Ann Rheum Dis* 2014; 73(4): 722–727.

72. Rueda-Gotor J, Llorca J, Corrales A, et al. Cardiovascular risk stratification in axial spondyloarthritis: carotid ultrasound is more sensitive than coronary artery calcification score to detect high-cardiovascular risk axial spondyloarthritis patients. *Clin Exp Rheumatol* 2018; 36(1): 73–80.

73. Piepoli MF, Hoes AW, Agewall S, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: the Sixth Joint Task Force of the European Society of Cardiology and other societies on cardiovascular disease prevention in clinical practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J* 2016; 37: 2315–2381.

74. Petri MA, Barr E and Magder LS. Development of a systemic lupus erythematosus cardiovascular risk equation. *Lupus Sci Med* 2019; 6: e000346.

75. Urowitz MB, Ibanez D, Su J, et al. Modified Framingham risk factor score for systemic lupus erythematosus. *J Rheumatol* 2016; 43(5): 875–879.

76. Willeit P, Thompson SG, Agewall S, et al. Inflammatory markers and extent and progression of early atherosclerosis: meta-analysis of individual-participant-data from 20 prospective studies of the PROG-IMT collaboration. *Eur J Prev Cardiol* 2016; 23(2): 194–205.

77. Ikonomidis I, Makavos G, Katsimbri P, et al. Imaging risk in multisystem inflammatory diseases. *JACC Cardiovasc Imaging* 2019; 12(12): 2517–2537.

78. Sandhu VK, Wei J, Thomson LEJ, et al. Five-year follow-up of coronary microvascular dysfunction and coronary artery disease in systemic lupus erythematosus: results from a community-based lupus cohort. *Arthritis Care Res* 2020; 72(7): 882–887.

79. Galie N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension: the joint task force for the diagnosis and treatment of pulmonary hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Respir J* 2015; 46: 903–975.

80. Coghlan JG, Denton CP, Grunig E, et al. Evidence-based detection of pulmonary arterial hypertension in systemic sclerosis: the DETECT study. *Ann Rheum Dis* 2014; 73(7): 1340–1349.

81. Solomon DH, Reed GW, Kremer JM, et al. Disease activity in rheumatoid arthritis and the risk of cardiovascular events. *Arthritis Rheum* 2015; 67(6): 1449–1455.

82. Ashai S and Harvey NC. Rheumatoid arthritis and bone health. *Clin Med* 2020; 20: 565–567.

83. Adami G and Saag KG. Osteoporosis pathophysiology, epidemiology, and screening in rheumatoid arthritis. *Curr Rheumatol Rep* 2019; 21: 1–10.

84. Matsumoto T and Itsuro E. RANKL as a target for the treatment of osteoporosis. *J Bone Miner Metab* 2021; 39(1): 91–105.

85. Deal C. Bone loss in rheumatoid arthritis: systemic, periarticular, and focal. *Curr Rheumatol Rep* 2012; 14(3): 231–237.

86. Messina OD, Vidal LF, Wilman MV, et al. Management of glucocorticoid-induced osteoporosis. *Aging Clin Exp Res* 2021; 33: 793–804.

87. Adami A, Fassio A, Rossini M, et al. Osteoporosis in rheumatic diseases. *Int J Mol Sci* 2019; 20: 5867.

88. Ozen G, Pedro S, Wolfe F, et al. Medications associated with fracture risk in patients with rheumatoid arthritis. *Ann Rheum Dis* 2019; 78: 1041–1047.

89. Shin A, Park EH, Dong YH, et al. Comparative risk of osteoporotic fracture among patients with rheumatoid arthritis receiving TNF inhibitors versus other biologics: a cohort study. *Osteoporos Int* 2020; 31(11): 2131–2139.

90. Wang X, Yan S, Liu C, et al. Fracture risk and bone mineral density levels in patients with systemic lupus erythematosus: a systematic review and meta-analysis. *Osteoporos Int* 2016; 27(4): 1413–1423.

91. Cramarossa G, Urowitz MB, Su J, et al. Prevalence and associated factors of low bone mass in adults with systemic lupus erythematosus. *Lupus* 2017; 26: 365–372.

92. Bultink IEM. Bone disease in connective tissue disease/systemic lupus erythematosus. *Calcif Tissue Int* 2018; 102(5): 575–591.

93. Briot K and Roux C. Inflammation, bone loss and fracture risk in spondyloarthritis. *RMD Open* 2015; 1(1): e000052.

94. Vosse D, Landewé R, van der Heijde D, et al. Ankylosing spondylitis and the risk of fracture: results from a large primary care-based nested case control study. *Ann Rheum Dis* 2009; 68(12): 1839–1842.

95. Ghozlani I, Ghazi M, Nouijai A, et al. Prevalence and risk factors of osteoporosis and vertebral fractures in patients with ankylosing spondylitis. *Bone* 2009; 44(5): 772–776.

96. Yoo BW, Jung SM, Song JJ, et al. Prevalence of osteopenia in drug-naive patients with antineutrophil cytoplasmic antibody–associated vasculitis: a monocentric study. *J Clin Rheumatol* 2021; 27: e330–e335.

97. Walsh M, Merkel PA, Peh CA, et al. Plasma exchange and glucocorticoids in severe ANCA-associated vasculitis. *N Engl J Med* 2020; 382: 622–631.

98. Calderón-Goercke M, Castañeda S, Aldasoro V, et al. Tocilizumab in giant cell arteritis: differences between the GiACTA trial and a multicentre series of patients from the clinical practice. *Clin Exp Rheumatol* 2020; 38(Suppl. 124): 112–119.

99. Pereira RM, Carvalho JF and Canalis E. Glucocorticoid-induced osteoporosis in rheumatic diseases. *Clinics* 2010; 65: 1197–1205.

100. Hootman JM, Helmick CG, Barbour KE, et al. Updated projected prevalence of self-reported doctor-diagnosed arthritis and arthritis-attributable activity limitation among US adults, 2015-2040: projected prevalence of arthritis in the US, 2015-2040. *Arthritis Rheum* 2016; 68: 1582–1587.

101. Lee YH, Ko PY, Kao SL, et al. Risk of total knee and hip arthroplasty in patients with rheumatoid arthritis: a 12-year retrospective cohort study of 65,898 patients. *J Arthroplasty* 2020; 35(12): 3517–3523.

102. Guldberg-Møller J, Cordtz RL, Kristensen LE, et al. Incidence and time trends of joint surgery in patients with psoriatic arthritis: a register-based time series and cohort study from Denmark. *Ann Rheum Dis* 2019; 78(11): 1517–1523.

103. Mukherjee S, Culliford D, Arden N, et al. What is the risk of having a total hip or knee replacement for patients with lupus? *Lupus* 2015; 24: 198–202.

104. Kremers HM, Larson DR, Crowson CS, et al. Prevalence of total hip and knee replacement in the United States. *J Bone Joint Surg Am* 2015; 97: 1386–1397.

105. Singh JA, Yu S, Chen L, et al. Rates of total joint replacement in the United States: future projections to 2020-2040 using the National Inpatient Sample. *J Rheumatol* 2019; 46(9): 1134–1140.

106. Johnson CA, White CC, Kunkle BF, et al. Effects of the obesity epidemic on total hip and knee arthroplasty demographics. *J Arthroplasty* 2021; 36(9): 3097–3100.

107. Barbour KE, Helmick CG, Boring M, et al. Vital signs: prevalence of doctor-diagnosed arthritis and arthritis-attributable activity limitation — United States, 2013–2015. *Morb Mortal Wkly Rep* 2017; 66: 246–253.

108. Patel AP, Gronbeck C, Chambers M, et al. Gender and total joint arthroplasty: variable outcomes by procedure type. *Arthroplast Today* 2020; 6(3): 517–520.

109. Johnson RL, Abdel MP, Frank RD, et al. Impact of frailty on outcomes after primary and revision total hip arthroplasty. *J Arthroplasty* 2019; 34(1): 56.e5–64.e5.

110. Cook MJ, Lunt M, Board T, et al. The impact of frailty on short-term mortality following primary total hip and knee arthroplasty due to osteoarthritis. *Age Ageing* 2022; 51: afac118.

111. Ethgen O, Bruyère O, Richy F, et al. Health-related quality of life in total hip and total knee arthroplasty. A qualitative and systematic review of the literature. *J Bone Joint Surg Am* 2004; 86: 963–974.

112. Chung HK, Wen SH, Chang WC, et al. Acute surgical site infection after total knee arthroplasty in patients with rheumatoid arthritis versus osteoarthritis. *Sci Rep* 2021; 11: 22704.

113. Shah UH, Mandl LA, Mertelsmann-Voss C, et al. Systemic lupus erythematosus is not a risk factor for poor outcomes after total hip and total knee arthroplasty. *Lupus* 2015; 24: 900–908.

114. Zhou VY, Lacaille D, Lu N, et al. Has the incidence of total joint arthroplasty in rheumatoid arthritis decreased in the era of biologics use? A population-based cohort study. *Rheumatology* 2022; 61: 1819–1830.

115. Tung KK, Lee YH, Lin CC, et al. Opposing trends in total knee and hip arthroplasties for patients with rheumatoid arthritis vs. the general population-a 14-year retrospective study in Taiwan. *Front Med* 2021; 8: 640275.