Chapter

Myopenia and Musculoskeletal Aging in Rheumatoid Arthritis

Dan Xu, Jiake Xu and Lei Dai

Abstract

Rheumatoid arthritis (RA), the commonest inflammatory arthritis, is a debilitating disease leading to decreased functional capacity, social disability and reduced quality of life. RA affects multisystems with chronic inflammatory disease characterized by destructive synovitis and muscular dysfunction leading to premature musculoskeletal aging, which has been coined with many terms including myopenia, sarcopenia, cachexia, muscle failure and muscle wasting. Myopenia is described as the presence of clinically relevant muscle wasting due to any illness at any age, associated with impaired muscle function, increased morbidity and mortality. RA myopenia has significantly less muscle mass compared to the general population muscle loss showing preservation or slight increase in fat mass. RA myopenia is unique compared to chronic disease-related myopenia in cancer, chronic heart failure, kidney disease and chronic infection as it is rarely accompanied by a net weight loss. RA myopenia has younger-age onset compared to elderly primary sarcopenia, while higher-grade inflammation has been considered as the pathophysiology of muscle wasting. Research, however, indicates that inflammation itself cannot fully explain the high prevalence of muscle wasting in RA. This chapter aims to review the literature on the casual relationships among RA myopenia, premature musculoskeletal aging and management strategies to delay musculoskeletal aging.

Keywords: myopenia, rheumatoid arthritis, musculoskeletal aging, chronic inflammation

1. Musculoskeletal aging in the healthy elderly

Muscle mass decreases on advancing age with men losing more absolute and relative muscle mass, especially most prevalent in the seventh decade and beyond [1]. After the age of 50, approximately 1–2% per year of muscle mass is lost, and this age-related reduction in muscle mass and strength is accompanied by intramuscular fat accumulation, muscle atrophy (especially the type IIa fibers), decreased satellite cell proliferation and differentiation capacity, and reduction in motor unit quantity. This muscle remodeling results in changes in muscle architecture that is believed to play a key role in the loss of muscle force and power characteristic of advanced age [2, 3]. Mitchell's group [1] reported only 0.5–1.0% loss of muscle mass per year after 70 and a 4.7% loss compared with peak muscle mass in men and 3.7% decrease for women per decade. Muscle strength simultaneously declines by 10–15% per decade up to 70 years of age, while the muscle strength loss accelerates to between 25 and 40% per decade [4, 5]. Frailty may be regarded as a condition

of transition from health to disability during aging. The concept of frailty is often defined as the presence of fatigue, slowness, weakness, low physical activity and exhaustion, which are all mainly related to muscle loss [6].

2. Prevalence of musculoskeletal aging in rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by erosive arthritis and systemic organ involvement with the worldwide prevalence of roughly 5 per 1000 adults. The disease may affect all ages and both sexes; usually, it is seen in young women aged 25–45. The peak incidence is in the sixth decade with recent studies showing that RA is among the most common inflammatory disease in the elderly, accounting for 2% of the geriatric population [7]. The general consensus in the literature is defining rheumatoid arthritis onset after 65 years of age being known as elderly onset RA (EORA). EORA incidence and prevalence in different population-based studies in the world may vary widely, depending on sex and ethnicity [8]. One study showed the incidence rate of RA per 100,000 population over the age of 60 being 9.1 in men and 14.5 in women [9]. A USA study showed the prevalence of RA being 0.5–1%, with 2% in the population over 60 years [10]. The UK-based database Norwalk Arthritis Research (NOAR) showed the incidence of RA increasing with age [11]. The Chinese pooled prevalence showed the estimated population prevalence of RA being 0.37% with 10% elderly onset RA [12]. This fact will likely increase the number of patients with EORA in the coming years to encourage research into the impact of ethnic and geographic differences on the management of RA.

3. Myopenia, sarcopenia, cachexia, muscle failure and muscle wasting disease as one concept in muscle aging of rheumatoid arthritis

3.1 Myopenia and sarcopenia

Myopenia is a relatively new term [13] describing the presence of clinically relevant muscle wasting due to any illness and at any age, associated with clinically relevant degree of muscle wasting, impaired muscle function and increased risks of morbidity or mortality. This term would translate more sufficiently and specifically in clinical settings than sarcopenia, which was introduced in 1988 with the original definition being a "muscle loss" of the appendicular muscle mass in the older people as measured by dual-energy X-ray absorptiometry [14]. In 2010, the European Working Group on Sarcopenia for Older Persons recommended a new operational definition of sarcopenia of aging (primary sarcopenia) including the presence of low muscle mass, low muscle strength and low muscle function and performance [15]. In 2018, two pieces of consensus evidences on sarcopenia of aging were published to combine the update by the European Working Group on Sarcopenia [16] with management of sarcopenia of aging by the International Clinical Practice Guidelines for Sarcopenia [17]. The consensus statement confirms the requirements of low muscle strength (low muscle quality), low muscle mass (low muscle quantity) and muscle functional impairment (low muscle performance) for the clinical diagnosis. Secondary sarcopenia, a similar term to myopenia, is associated with the international consensus definitions specific to malignant sarcopenia in the recent sarcopenia positional review [18]. There are several points of relevance regarding age-related (primary sarcopenia) and disease-related (secondary sarcopenia) loss

of muscle mass. Loss of appendicular skeletal muscle mass with aging (primary sarcopenia) occurs continuously in the order of ~5% in men and somewhat lower in women after reaching peak muscle mass in young adulthood at about 30 years of age by a variety of longitudinal observational studies [19, 20]. Another interesting terminology related to secondary sarcopenia is sarcopenic obesity, and the copresence of sarcopenia and obesity has been considered a more deleterious body composition phenotype [21]. In addition to a myriad of cardio-metabolic outcomes related to the effects of fat tissue, higher proportions of fat mass might further affect muscle quality and increase the risk of disability and mortality [22]. A recent Brazil study [23] concluded sarcopenic obesity, but obesity alone was not associated with obstructive sleep apnea (OSA). Both obesity and sarcopenic obesity but not sarcopenia were associated with nocturnal hypoxemia, suggesting a complex pathophysiologic relationship between adverse body composition states and OSA. There are cultural difference in sarcopenic obesity with recent published data of Chinese RA patients, which indicated the lower prevalence of obesity (Chinese 4.2% vs. Westerners 21.4–34.7%) and higher prevalence of underweight (Chinese 17.7% vs. Westerners 1.1–2.2%). Taking together, secondary sarcopenia or myopenia has a non-linear muscle loss curve with a considerably greater magnitude than the linear curve seen in primary sarcopenia. RA patients have significantly less muscle mass compared to the general population, leading to the statement (**Figure 1**) that myopenia is a form of premature disease-related muscular aging in association with connective tissue diseases like rheumatoid arthritis and other chronic diseases shown in **Figure 1**.

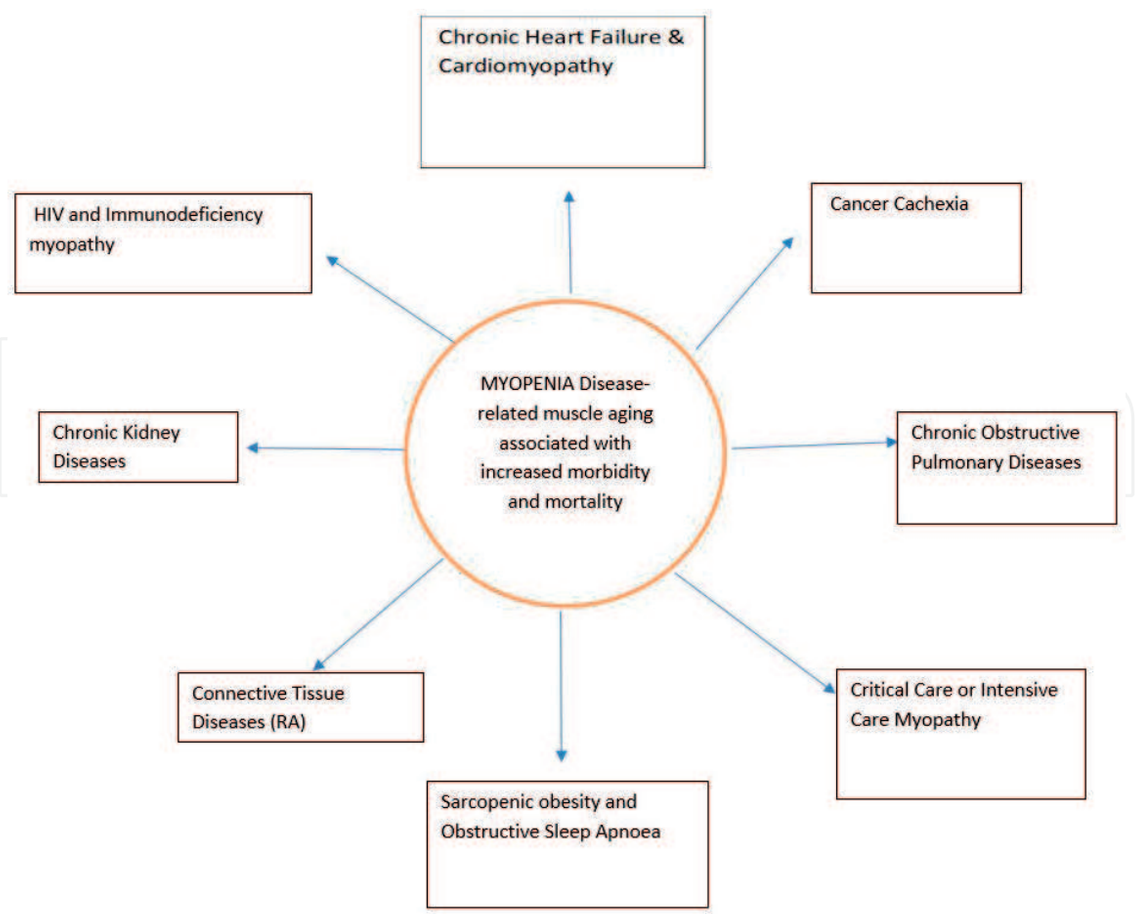

Figure 1.
Myopenia in association with connective tissue diseases like rheumatoid arthritis and other chronic diseases.

3.2 Cachexia, muscle failure and muscle wasting disease

Rheumatoid arthritis cachexia (RAC) is characterized by high degrees of muscle mass loss and muscle strength loss, associated with preservation or slight increase in fat mass [24]. RAC is unique in comparison to other forms of cachexia observed in cancer, chronic heart failure, kidney disease and chronic infection as it is rarely accompanied by a net weight loss [25]. RAC also differs from primary sarcopenia in the elderly as it occurs at much younger age associated with significantly higher muscle mass loss [26]. Higher-grade inflammation has been considered as the central component of the pathophysiology and the key driver of muscle wasting. More recent findings, however, indicate that inflammation on its own cannot fully explain the high prevalence of muscle wasting in RA. Thus, two lifestyle factors including nutrition and physical activity have also been studied to indicate that they play a significant role in muscle wasting in RA, but again neither of these factors seems to be able to fully explain the condition. Oxidative stress is one of the major mechanisms thought to contribute to the development and progression of RA, but its potential contribution to muscle wasting in these patients has received limited attention. Oxidative stress has been shown to promote muscle wasting in healthy populations and people with several chronic conditions. Moreover, all of the aforementioned potential contributors to muscle wasting in RA (i.e., inflammation, nutrition and physical activity) may promote pro- or anti-oxidative mechanisms. Muscle failure is another new term describing the combination of primary and secondary sarcopenia, leading to a more relevant functional definition of premature muscle aging related to rheumatoid arthritis, RA-related muscle failure instead of myopenia. This review will put more emphasis to highlight the important clinical implication of myopenia and premature muscular aging and discuss the various management strategies of delaying musculoskeletal aging in RA, including muscle regeneration *via* reduction in oxidative stress and early control of inflammation via lifestyle and pharmacological interventions.

4. Genetics of RA and muscle aging

RA develops in individuals with a genetic association in RA, which is the presence of DRB1 locus in the HLA class 2 gene. The RA-associated DRB1 alleles share a linear sequence of amino acids between positions 70 and 74 in the HLA-DRB1 chain of the HLA-DRa/b heterodimer, which has led to the 'shared epitope' (SE) hypothesis [27], posing a risk factor for RA development. Jnhi DRB1 allele was associated with early onset of disease, radiological erosion and extra-articular findings [28]. The results of studies investigating genetic predisposition in EORA are inadequate and contradictory [29]. RA-associated DRB1 alleles show differences in early and late onset RA as well as ethnic variants. A Spanish study found that YORA was related to DRB1/04, while EORA was associated with DRB1/01 [30]. This study also found that increased DRB1–13/14 frequency was detected in patients with seronegative EORA and polymyalgia rheumatica (PMR). Another prospective study established the facts that a relationship was found between PMR and DRB1*0101/0102/0401, while seronegative EORA was associated with DRB1-0401. Kim and colleagues investigated the impact of HLA-DRB1 and HLA-DQB1 genes on susceptibility to disease and disease severity in EORA and YORA patients [31]. Alleles encoding the common epitope were detected less frequently in EORA compared with YORA with the effect of the common epitope and HLA-DQ*04 alleles being shown to be less significant. In comparison with YORA, EORA has also been found to have less common epitope presence and less radiological progression.

Hellier and colleagues investigated the effect of the HLA-DRB1 gene on disease susceptibility and disease severity in EORA and YORA [32] and demonstrated HLA-DRB1/04-related alleles were not closely associated in EORA. Thus, it is suggested that the impact of these genes on the susceptibility to disease in EORA is not very important. Wu and colleagues showed that the DRB1/04 allele was detected in half of the EORA population, while the DRB1/04 frequency was 92% in patients with RA starting before 30 years of age [33].

In terms of genetic contribution and impact on the individual variability in muscle aging phenotypes literature on specific gene variants, it remained controversial and no solid evidence exists supporting the existence of an 'unfavorable' genotype associated with accelerated age-related sarcopenia or loss of independent function [34]. Although the ACTN3 R577X polymorphism is the only structural gene for which a clear genotype effect has been shown in human muscle phenotypes, especially for athletic women, there is controversy with regard to which allele (R or X) plays a potential 'favorable' role in aging. The MSTN K153R variation is possibly the strongest candidate to explain variance among muscle phenotypes in the elderly, yet more research is still needed with large cohorts owing to the very low population frequency of the 'unfavorable' 153R allele. Recent evidence [34] indicates that age-related declines in muscle phenotypes are likely polygenic traits and thus not reducible to specific polymorphisms, suggesting that future studies should consider the association between muscle phenotypes in older people including complex gene-gene interactions, interactions between genetic variants that might not influence muscle phenotypes individually and the interaction between genes and chronic disease like rheumatoid arthritis and lifestyle risk factors such as physical activity. It is important to determine those genetic factors that interact with aging and thus modulate functional capacity and genetic predisposition of myopenia in rheumatoid arthritis. It would be also clinically relevant to identify 'unfavorable' genotypes associated with myopenia in rheumatoid arthritis.

5. Pathogenesis of myopenia and musculoskeletal aging in RA

Two major subtypes of RA are classified according to the presence or absence of anti-citrullinated protein antibodies (ACPAs). Citrullination is catalyzed by the calcium-dependent enzyme peptidylarginine deiminase (PAD), changing a positively charged arginine to a polar but neutral citrulline as the result of a post-translational modification. ACPAs can be detected in approximately 67% of RA patients and serve as a useful diagnostic reference for patients with early, undifferentiated arthritis and provide an indication of likely disease progression through to RA [35, 36]. The ACPA-positive subset of RA has a more aggressive clinical phenotype compared to ACPA-negative subset of RA [37]. It is reported that ACPA-negative RA has different genetic association patterns [37] and differential responses of immune cells to citrullinated antigens [38] from those of ACPA-positive subset. In terms of standard treatment [39–41], less effective treatment response of methotrexate (MTX) or rituximab was observed in ACPA-negative subset. Future studies are needed on the potential pathophysiology difference between the two subsets, while this chapter will focus on the ACPA-positive subset of RA and divide the onset and progression of RA process into the above-mentioned EORA and YORA. Since the clinical, genetic and laboratory differences between EORA and YORA are not understood yet, the immunological and hormonal changes in the elderly population may be responsible for the physiological process characterized by reduced T-cell proliferation, reduced antibody synthesis to vaccination and elevated proinflammatory cytokine levels. Immune system changes include T-cell phenotype alteration,

reduction in specific immune response, apoptosis defects, cytokine imbalance and inadequate antigen presentation. With increasing age, there is a decrease in the protective immunological response, while the reaction to autoantigens is increasing [42]. In addition, self-tolerance mechanism disorders occur. As a result of thymus involution in senescence, changes in T-cell composition, decrease in T-cell proliferation and cytokine synthesis, as well as decreased antibody synthesis after vaccination, were seen. In one study, elevated interleukin (IL)-6 secretion was associated with dehydroepiandrosterone and androstenedione synthesis in patients with EORA [43]. The acute onset and increased acute phase response seen in EORA may be explained by increased IL-6 levels. Punzi and colleagues showed elevated IL-6 as acute onset and increased acute phase response in the EORA synovial fluid compared with YORA, suggesting the role of IL-6 while no differences were detected in IL-1 and IL-8 levels [44]. Different immunoregulatory mechanisms may be at work in the pathogenesis of RA seen in different age groups with one study by Gamerith and colleagues showing a significantly increased anti-IgG-Fab/free aFab ratio in patients with YORA, compared with EORA, leading to increased rheumatoid factor (RF) presence [45]. Myopenia in RA will be mediated by a similar mechanism of rising IL-6, leading to premature muscle aging in YORA, while acute-onset-induced long-term muscle damage is equivalent to premature muscle aging in EORA. Further research is required to unlock the mechanism of premature muscular aging in RA patients.

6. Clinical features of myopenia in rheumatoid arthritis

Myopenia in rheumatoid arthritis is a similar term to terms described above including secondary sarcopenia, rheumatoid arthritis cachexia and muscle failure or muscle wasting in rheumatoid arthritis. The clinical features follow the two forms of rheumatoid arthritis including EORA and YORA with their distinctive features. EORA has three distinct clinical patterns [46] with the most common clinical form (70%) displaying RF positivity, joint erosions and worse prognosis than YORA, while the second form (25%) is a PMR-like form with proximal limb joint involvement characterized by RF negativity, being associated with acute onset, lack of joint erosions and good prognosis. Non-erosive polyarthritis may be present in 25% of patients with PMR as one of the main differential diagnoses [47]. The presence of metacarpophalangeal (MCP)/proximal interphalangeal (PIP) joint arthritis with proximal limb joint involvement is considered a predictive factor for seronegative EORA. The third EORA pattern is featured by clinical and prognostic similarity to RS3PE syndrome [48] with sudden onset, wrist tenosynovitis, common pitting edema in the hands, HLA-B27 positivity and spontaneous remission within 3–18 months. EORA is not limited to the differentiate diagnosis of PMR, but also associated with other diseases including crystal arthritis, septic arthritis, sarcoidosis and hepatitis C [49]. In many studies [50, 51], simultaneous small and large joint involvement is frequently seen at the onset of the disease, while RF and anti-CCP positivity are seen at similar and/or slightly lower rates in comparison with YORA. Acute onset, PMR-like symptoms, less rheumatoid nodule and RF positivity were detected in EORA compared with YORA. Patients with EORA had a lower joint score and a higher Health Assessment Questionnaire (HAQ) score. A recent study [52] reported the clinical and demographic characteristics of Turkish patients with EORA displaying shoulder joint involvement being more frequent in EORA, while PIP, MCP, elbow and ankle joint involvement were more common in YORA. RA deformities, Sjögren syndrome (SjS) and lung involvement are less common in EORA. Weight loss, myalgia, lymphadenopathy and PMR-like symptoms

were also more frequent in EORA, while the antibody profile (RF, ANA, anti-Ro and anti-La) was detected less frequently in EORA. In contrast, anemia of chronic disease, ESR and CRP elevation were more common in a study reported by van der Heijde and colleagues [53]. Another aggressive, destructive EORA form of EORA having more frequent acute onset, initially small and large joint involvement, PMR-like patterns and radiological narrowing of the joint space was reported by Lance and colleagues with radiographic erosive changes [54]. In this report, the patients are characterized by polyarticular small joint involvement, rapid progression, hand/wrist erosions and early hand function loss as well as 63% of these patients reported secondary SjS compared with 25% in patients with YORA. More recently, myopenia has been reported to be very common in Chinese RA patients that is associated with functional limitation and joint damage in RA [55]. In another report at the 2019 American College of Rheumatology meeting, myopenia, equivalent to body composition disorder in elderly Chinese patients with RA, showed that elderly female patients with myopenia were associated with severe joint damage in rheumatoid arthritis [56]. These studies reflected both the cultural and gender diversity of myopenia in RA.

7. Laboratory findings in myopenia in RA

It has been well documented that lower hemoglobin and higher ESR and CRP were detected in EORA in comparison with YORA [57]. In some studies, RF and anti-CCP antibody positivity were reported less frequently in EORA, while in other studies, the frequency of these antibodies was found to be similar in both groups [51, 53, 58]. Chen and colleagues compared the pro-inflammatory cytokine levels of patients with EORA and YORA [59] demonstrating that higher levels of IL-6 and lower levels of tumor necrosis factor α (TNFα) were detected in EORA, associated with higher IL-6 levels being detected in patients with EORA and PMR-like symptoms. Multivariate analysis showed that high IL-1 levels were associated with anti-CCP antibodies, while high TNFα levels were associated with constitutional symptoms in patients with EORA. In comparison with YORA, acute onset, constitutional symptoms and comorbidities were more frequent in patients with EORA.

8. Prognosis of myopenia in RA

There is no direct evidence for discussion with respect to the impact of myopenia on the prognosis of RA. The prognosis of RA in terms of RA's age of onset remains unclear with some studies showing EORA with better prognosis compared with YORA, while others report that they are similar or worse. The above contradictory results may be due to different disease durations between groups examined, bias in patient selection, and different frequencies of seropositivity between younger and older patients. In one study, persistent arthritis was seen in 39% of seropositive patients, while in seronegative patients, this rate was only 6% [60]. In another study, more swollen joints, radiological damage and mortality were reported in seropositive patients in comparison with seronegative patients [61]. In other words, RF and anti-CCP antibodies are considered poor prognostic markers in patients with EORA. Krams and colleagues compared the characteristics of patients with EORA and YORA in the ESPOIR cohort containing 681 patients with RA [62], and the one-year remission rates were higher in the patients with YORA than those with EORA showing more erosion and high HAQ scores in patients with EORA. As a result, at the end of the third year, patients with YORA had higher remission rates,

less radiographic progression and lower HAQ scores compared with patients with EORA. A Korean study evaluated 3169 Korean patients with RA [58] and showed that the 486 patients with RA that started when they were over 60 years old were considered to have EORA and it has been found to be an independent risk factor for functional disability. In one study, the presence of acute pitting swelling in the hands at the onset of the disease was shown to be a good prognostic factor [60] with EORA presenting with pitting edema having fewer erosions compared with patients with EORA without pitting edema. In terms of EORA mortality related to myopenia, there was a statistically significant increase in mortality rates in patients with seropositive EORA compared with the general population [57], while there was not significant difference in patients who were seronegative.

9. Treatment and management of myopenia in RA

Management of myopenia in RA will translate the latest research evidence of treatment strategies for rheumatoid arthritis. These strategies include the optimization of lifestyle and risk factor modifications including nutrition and exercise; pharmacological interventions include early administration of disease-modifying antirheumatic drugs (DMARDs); and targeted strategies have been able to prevent radiological progression, reduce morbidity and mortality, and increase functional capacity [63, 64].

10. Exercise and myopenia/cachexia in rheumatoid arthritis

RA and exercise have been thoroughly reviewed [65] to indicate the reduced and compromised exercise capacity in comparison with normal people due to their RA manifestations of pain, stiffness, structural joint damage, bone density loss and muscle weakness [66, 67]. It is well established that physical exercise programs promote prolonged improvements [68] without inducing harmful effects on disease activity and joint damage [69]. Recent evidence [65] has examined different modalities of exercises including resistance training, aerobic training and combination of the two modalities. Aerobic training consists of cycling, aquatics, dancing, walking and running. The final messages show that exercise is effective in reversing joint damage in RA patients as long as RA-specific considerations are being taken into account when developing exercise programs aiming to reduce CVD risk and improve quality of life and maintaining activity of daily living functions of RA patients. In another study [70] describing myopenia/cachexia and exercise types for treatment, intensive progressive resistance training (PRT) can increase lean mass, reduce fat mass, increase strength and improve function. PRT is the most effective exercise to improve skeletal muscle size and strength, even safe when performed at high intensity with RA patients. Resistance training increases tendon stiffness and strengthens connective tissue, while cyclic loading (e.g., walking, cycling and strength endurance exercises) enhances cartilage integrity and joint lubrication as well as mobility exercises increase range of motion. In terms of symptom control in RA patients, exercise can reduce pain and morning stiffness and even reduce fatigue as well as improve functional ability and psychological well-being without exacerbating disease activity. The review also discusses the improvement of patient perceptions regarding the effects and benefits of exercise, clarifies specific exercise recommendations and considers methods of overcoming individual barriers to exercise. A recent study showed that hydrotherapy had a positive role in reducing pain and improving health status of RA patients [71]. All RA patients should be

encouraged to include some form of aerobic and resistance exercise training as part of their routine care. More research is still required on the optimal and individualized frequency, intensity, time and types (FITT model) of exercises, or when it requires a combination of types as well as how best to incorporate exercise into the lives of RA patients across the variable course of the disease. Large cohort studies will be required to examine the potential ethnic differences in terms of myopenia and muscle aging in diverse cultures such as in China, India or Africa.

11. Management of frailty and prefrailty in rheumatoid arthritis myopenia

Frailty, which was originally considered a geriatric syndrome [72], is associated with reduced muscle strength, exhaustion and high inflammatory markers [73, 74], leading to perpetuation of the frailty and prefrailty cycle associated with different frailty assessment tools [75, 76]. Frailty and myopenia share a common cardinal clinical feature of reduced muscle strength. A recent study [77] showed that frailty and prefrailty are common in RA patients of younger age and are more prevalent than expected. As the prevalence of frailty increases with age, this study indicates that it is important to counteract frailty for the treatment of myopenia in RA patients. A very interesting aspect for further research would be to assess the frailty status in a large sample size to investigate if the frailty score is lower in RA patients who have entered into permanent remission after early treatment, whereby they did not develop any joint damage, compared to age- and sex-matched patients who have been treated less aggressively.

12. Myopenia, heart failure and premature myocardial aging in RA

RA and other autoimmune chronic inflammatory disorders including psoriasis and inflammatory bowel diseases have been well documented to be associated with considerably increased cardiovascular morbidity and mortality in comparison with the background population [78–82]. In particular, the cardiovascular disease risk in RA patients appears to be comparable with that found in type 2 diabetes mellitus patients [83–85]. Conventional cardiovascular risk factors including hypertension, obesity, dyslipidemia and diabetes mellitus with RA-specific risk factor of increased systemic inflammation have been implicated to contribute significantly [81, 86].

Heart failure (HF), an alternative term describing myopenia in the cardiac muscle, has been shown by numerous public health studies to be associated with increased inflammation and a high prevalence of cardiovascular risk factors [87, 88]. The proinflammatory cytokines of HF promote myocardial damage leading to myopenia of cardiac muscle and other pathogenic manifestations through an array of mechanisms including increased arterial stiffness and endothelial dysfunction [89–95]. A number of review and population studies have examined the risk of developing HF in RA patients and found that RA-specific HF can be independent of cardiovascular risk factors [89, 93, 96, 97]. One of the commonest risk factors and potential cause of HF is ischemic heart disease, which was not shown to be responsible for the increased risks of HF in rheumatoid arthritis. This paper [93] also demonstrated that the increased risks of non-ischemic HF in RA presented early in association with RA severity. A more recent Danish cohort study [98] aimed to investigate the risk of incident HF in RA patients indicated that rheumatoid arthritis was associated with a 30% increased hospitalization for heart failure in

comparison with the general population. The clinical Implications of these findings add to the existing evidence that rheumatoid arthritis may be a clinically relevant risk factor for heart failure and premature cardiac muscle aging in RA patients. Future studies examining the value of more extensive screening of RA patients for heart failure are warranted.

In terms of the potential mechanism for increased risks of HF in early course of RA, RA has been associated with left ventricular concentric remodeling and systolic and diastolic left ventricular dysfunction [89, 90, 93, 97]. RA patients are more likely to display significantly elevated levels of circulating cardiac biomarkers including troponins, pro-B-type natriuretic peptides, which are recognized as important prognostic markers of cardiac diseases, especially HF [99]. Thus, it is highly conceivable that chronic systemic inflammation in RA may confer an increased risk of HF and premature myocardial aging that is independent of traditional cardiovascular risk factors.

13. Myopenia and pharmacological intervention in RA

Delaying myopenia and premature muscle aging in RA patients is closely related to the age of onset and preclinical staging of RA. While there are no direct evidences specifically evaluating the impact of pharmacological interventions including synthetic DMARDS and biologics on the management of myopenia in RA, the European League Against Rheumatism guideline advocates early aggressive treatment with these synthetic DMARDS and biologics via their direct effect on reducing inflammation for the purpose of reducing myopenia, delaying premature muscle aging in RA and decreasing cardiovascular morbidity and mortality in RA [100, 101]. These agents are also expected to exert their benefits via their direct effect on reducing inflammation, subsequently improving joint inflammation and function and potentially leading to increased levels of physical activity with consequent reduction of other risk factors including diabetes mellitus and hypertension [100, 101]. A recent study also demonstrates the potential mechanism of how synthetic DMARDS and biologics reduce the risks of sudden cardiac death in RA patients [100].

Identifying a preclinical stage and a growing understanding of the natural history and mechanisms of RA development, alongside new potential pharmacological interventions, shape the prospect that myopenia with premature muscle aging in RA might be preventable in future [102]. The current treatment principles for established RA involve symptomatic management and disease modification. A meta-analysis of 12 published studies confirmed that patients receiving delayed DMARDs therapy were at higher risk of developing radiographic joint space narrowing and bony erosions [103] associated with myopenia in RA with a recent cross-sectional study [55]. In poorly controlled RA patients, bony erosions become more pronounced on radiographs within 2 years of onset and these erosive changes are predictive of poorer functional outcome [104]. In a patient with otherwise unexplained new onset polyarthritis, an urgent referral to a rheumatologist is thus mandatory to confirm an RA diagnosis and early initiation of a DMARDs-based treatment plan aiming for disease remission with delaying myopenia in RA and preventing deformity. Oral corticosteroids are potent and effective anti-inflammatory drugs that may contribute to disease modification [105] to delay myopenia and promote healthy aging. However, this needs to be weighed up against its well-known adverse effects of osteoporosis. Symptomatic management remains the cornerstone interventions throughout the course of the disease with everyday practical measures to deal with the primary symptoms of joint stiffness including pain and fatigue via

the mechanism of reducing systemic inflammation. This chapter is not for detailed review and discussion of the pharmacological intervention of RA but endeavors to provide a table from the main author's previous review to summarize the modern pharmacological therapies for RA (**Table 1**) [106].

Classification	Name	Mechanism of action	Potential mechanisms	Side Effect	Reference
Conventional synthetic DMARDs	Methotrexate	Analog of folic acid	Folate-dependent processes; Adenosine signaling; Methyl-donor production; Reactive oxygen species; Adhesion-molecule expression; Cytokine profiles Eicosanoids and MMPs.	Increased liver enzymes, pulmonary damage.	83
	Leflunomide/ Teriflunomide	Pyrimidine synthesis inhibitor	DHODH-dependent pathway; Leukocyte adhesion; Rapidly dividing cells; NF-kB; Kinases; Interleukins; TGF-β.	Hypertension, diarrhea and nausea, hepatotoxicity.	153
	Sulfasalazine	Anti-inflammatory and immunosuppression	Cyclooxygenase and PGE2; Leukotriene production and chemotaxis; Inflammatory cytokines (IL-1, IL-6, TNF-α); Adenosine signaling; NF-kB activation.	Gastrointestinal, central nervous system, and hematologic adverse effect.	154
	Chloroquine /Hydroxychloroquine	Immunomodulatory effects	Toll-like receptors; Lysosomotropic action; Monocyte-derived pro-inflammatory cytokines; Anti-inflammatory effects; Cellular immune reactions; T cell responses; Neutrophils; Cartilage metabolism and degradation.	Gastrointestinal tract, skin, central nervous system adverse effect and retinal toxicity.	155
Biological DMARDs Antibody-based therapies					
TNF-α targeted therapy	Infliximab	TNF-α inhibitor	Phagocytosis and pro-inflammatory cytokines; Chemoattractant; Adhesion molecules and chemokines; Treg cell function; Function of osteoclasts, leukocytes, endothelial and synovial fibroblasts.	Infection (pneumonia and atypical tuberculosis) injection-site reaction.	
	Adalimumab			Hypertension.	
	Etanercept			Severe /anaphylactoid transfusion reaction.	156
	Golimumab				
	Certolizumab pegol				
B-cell targeted therapy	Rituximab	B cell depleting	Fc receptor gamma-mediated antibody-dependent cytotoxicity and phagocytosis; Complement-mediated cell lysis; antigen presentation; B cell apoptosis; Depletion of CD4 + T cells.	Infection, hypertension, hypogammaglobulinemia, viral reactivation, vaccination responses.	
	Ofatumumab			Late-onset neutropenia.	
	Belimumab	Inhibitors of B cell function		Severe/anaphylactoid transfusion reaction.	157
	Atacicept				
	Tabalumab				
T-cell targeted therapy	Abatacept	CD28/CTLA4 system	Autoantigen recognition; Immune cell infiltrate; T cells activation.	Infection, malignancy.	158
	Belatacept	CD80/CD86			
Interleukin targeted therapy	Tocilizumab	IL-6 inhibition	Innate and the adaptive immune system perturbation; Acute-phase proteins.	Infections (most notably skin and soft tissue), increases in serum cholesterol, transient decreases in neutrophil count and abnormal liver function.	159
	Anakinra	IL-1 inhibition	Inflammatory responses; Matrixenzyme.	Injection site reactions, infections, neutropenia, malignancy.	160
	Canakinumab				
	Rilonacept				
	Secukinumab	IL-17 inhibition	Mitochondrial function; Autophagosome formation.	Infections, nasopharyngitis, candidiasis, neutropenia, safety data of mental health is limited.	161
	Ixekizumab				
Growth and differentiation factors	Denosumab	RANKL inhibitor	Maturation and activation of osteoclast.	Low Ca2 + and phosphate in the blood, muscle cramps, cellulitis, and numbness.	162
	Mavrilimumab	GM-CSF inhibitor	Activation, differentiation, and survival of macrophages, dendritic cells, and neutrophils; T helper 1/17 cell; modulation of pain pathways.	Safety file needs further research.	163
Small molecules					
JAK pathway	Tofacitinib	JAK1 and JAK3 inhibitor	T-cell activation, pro-inflammatory cytokine production, synovial inflammation, and structural joint damage.	Zoster infection (advice is to vaccinate beforehand) and other potential side-effects should be monitored carefully through further study.	163, 164
	Baricitinib	JAK1 and JAK2 inhibitor			
	Filgotinib	JAK1 inhibitor			
Future drug and target	Toll like receptors;[165] Bruton's tyrosine kinase;[151] Phosphoinositide-3-kinase pathway;[166] Transforming growth factor-beta;[167] Neuropathways;[168] Dendritic cell[169]				

Table from Ref. [106]. Permission from Bone Research is pending.

Table 1.
Modern pharmacologic therapies for rheumatoid arthritis.

In terms of the age of onset of rheumatoid arthritis, the ultimate goal of RA treatment including EORA and YORA is to control the disease, delay myopenia and maintain functional capacity. As discussed above on genetics, clinical features, pathogenesis and prognosis of EORA and YORA, treatment of EORA should not be so different from treatment of YORA. The goal of treatment should be complete remission or low disease activity based on the principles of treat-to-target strategies. DMARDs used in YORA may also be safely used in the treatment of EORA as long as drug pharmacokinetics and pharmacodynamics in the elderly can be clinically considered with closely monitoring the drug side effect profile [107]. EORA has more comorbid diseases and high number of medications used and consequently increasing drug-drug interactions exacerbating the potential side effect profile [108]. DMARDs used in patients with EORA are limited and contradictory and are receiving less aggressive treatment based on data from patients with EORA in the CORONA database in comparison with those of age- and sex-matched patients with YORA [109]. The study [109] also showed that disease activity and disease severity were similar in both groups. Methotrexate (MTX) use was found to be higher in patients with EORA compared with those with YORA (63.9% vs. 59.6%), while mean MTX dose was found to be higher in patients with YORA. The number of patients using multiple conventional DMARDs or biological DMARDs was found to be lower in those with EORA compared with YORA. Treatment-related toxicity was similar in both groups, whereas toxicity due to MTX was found to be more frequent in the case of YORA. Despite similar disease duration, disease activity and severity, patients with EORA used combined conventional DMARDs and biological DMARDs less frequently compared with patients with YORA. It has been well documented that the age of onset determines the severity of the disease and the choice of treatment [110]. According to Swiss registries, the use of first-line corticosteroids was significantly higher in patients with EORA compared with those with YORA, in contrast to the much lower follow-up on the use of biological drugs [111]. Genevay and colleagues evaluated 1571 patients with RA receiving anti-TNFα drugs [112] and demonstrated similar changes with drug withdrawal rates and mean Disease Activity Score (DAS28) score changes in both groups at the end of the second year. Despite clinical responses, improvement in Health Assessment Questionnaire (HAQ) scores was significantly less in patients with EORA. TNF inhibitors were slightly less or equally effective in reducing disease activity in elderly compared with younger patients with HAQ scores showing less improvement in patients with EORA, especially in patients aged over 75 years [113]. There is limited evidence for the effectiveness of tocilizumab, abatacept, rituximab and tofacitinib in EORA. Tocilizumab was less effective in EORA compared with YORA, while the drug retention rate and discontinuation rates because of adverse events were similar between the two age groups [114]. There is no data on abatacept in EORA, while RCTs showed tofacitinib to be similarly effective in both EORA and YORA [115]. In terms of myopenia in both EORA and YORA, a recent study [116] indicates that EORA is characterized by more equal distribution of sex, higher frequency of acute onset with constitutional symptoms, more frequent involvement of large joints, and lower frequency of RF positivity. Earlier diagnosis, less erosive disease and less DMARD usage were reported as distinguishing patients with EORA from those with YORA. Further studies require the exploration of myopenia and its severity and impact on the prognosis of RA including both EORA and YORA, reflecting the above-mentioned concepts of secondary sarcopenia, cachexia and frailty with old age, potentially impacting RA prognosis in the presence of DMARD side effects.

14. Conclusion and future perspectives

Myopenia and premature muscular aging in RA are similar concepts, raising a lot of research questions in terms of mechanism, lifestyle intervention, comorbidity management and new pharmacological approach. The chapter provides the platform for a discussion about the new term of myopenia and its impact.

Author details

Dan Xu[1,2*], Jiake Xu[3] and Lei Dai[4]

1 Curtin Medical School, Faculty of Health Sciences, Curtin University, Perth, Australia

2 Department of Medical Education, The First Affiliated Hospital, Sun Yat-Sen University, Guangzhou, Guangdong, China

3 School of Biomedical Sciences, Faculty of Health and Medical Sciences, The University of Western Australia, Perth, Australia

4 Department of Rheumatology, Sun Yat-Sen Memorial Hospital, Sun Yat-Sen University, Guangzhou, Guangdong, China

*Address all correspondence to: daniel.xu@curtin.edu.au

References

[1] Mitchell WK, Williams J, Atherton P, Larvin M, Lund J, Narici M. Sarcopenia, dynapenia, and the impact of advancing age on human skeletal muscle size and strength; a quantitative review. Frontiers in Physiology. 2012;**3**:260

[2] Narici MV, Maffulli N. Sarcopenia: Characteristics, mechanisms and functional significance. British Medical Bulletin. 2010;**95**:139-159

[3] Thomas DR. Loss of skeletal muscle mass in aging: Examining the relationship of starvation, sarcopenia and cachexia. Clinical Nutrition. 2007;**26**(4):389-399

[4] 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. The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences. 2006;**61**:1059-1064

[5] Hughes VA, Frontera WR, Wood M, et al. Longitudinal muscle strength changes in older adults: Influence of muscle mass, physical activity, and health. The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences. 2001;**56**:B209-B217

[6] Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in older adults: Evidence for a phenotype. The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences. 2001;**56**(3):M146-M156

[7] Laiho K, Tuomilehto J, Tilvis R. Prevalence of rheumatoid arthritis and musculoskeletal diseases in the elderly population. Rheumatology International. 2001;**20**:85-87

[8] Alamanos Y, Voulgari PV, Drosos AA. Incidence and prevalence of rheumatoid arthritis, based on the 1987 ACR criteria: A systematic review. Seminars in Arthritis and Rheumatism. 2006;**36**:182-188

[9] Carbonell J, Cobo T, Descalzo MA, et al. The incidence of rheumatoid arthritis in Spain: Results from a nationwide primary care registry. Rheumatology. 2008;**47**:1088-1092

[10] 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. Arthritis & Rheumatology. 2003;**48**:917-926

[11] Symmonds DPM, Barrett EM, Bankhead CR, et al. The incidence of rheumatoid arthritis in the United Kingdom: Results from the Norfolk arthritis register. British Journal of Rheumatology. 1994;**33**:735-739

[12] Xiang YJ, Dai SM. Prevalence of rheumatic diseases and disability in China. Rheumatology International. 2009;**29**:481-490. DOI: 10.1007/s00296-008-0809-z

[13] Fearon K, Evans WJ, Anker SD. Myopenia—A new universal term for muscle wasting. Journal of Cachexia, Sarcopenia and Muscle. 2011;**2**:1-3. DOI: 10.1007/s13539-011-0025-7

[14] Rosenberg IH. Sarcopenia: Origins and clinical relevance. Journal of Nutrition. 1997;**127**(Suppl):990S-991S

[15] 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 and Ageing. 2010;**39**:412-423

[16] Cruz-Jentoft AJ, Bahat G, Bauer J, et al. Sarcopenia: Revised European

consensus on definition and diagnosis. Age and Ageing. 2019;**48**:16-31

[17] Dent E, Morley JE, Cruz-Jentoft AJ, et al. International clinical practice guidelines for sarcopenia (ICFSR): Screening, diagnosis and management. The Journal of Nutrition, Health & Aging. 2018;**22**:1148-1161

[18] Bauer J, Morley JE, Schols AMWJ, Ferrucci L, Cruz-Jentoft AJ, Dent E, et al. Sarcopenia: A time for action. An SCWD position paper journal of cachexia. Sarcopenia and Muscle. 2019;**10**:956-961

[19] Siparsky PN, Kirkendall DT, Garrett WE. Muscle changes in aging: Understanding sarcopenia. Sports Health. 2014;**6**:36-40

[20] Keller K, Engelhardt M. Strength and muscle mass loss with aging process. Age and strength loss. Muscles, Ligaments and Tendons Journal. 2013;**3**(4):346-350

[21] Molino S, Dossena M, Buonocore D, Verri M. Sarcopenic obesity: An appraisal of the current status of knowledge and management in elderly people. The Journal of Nutrition, Health & Aging. 2016;**20**:780-788

[22] Zamboni M, Mazzali G, Fantin F, Rossi A, Di Francesco V. Sarcopenic obesity: A new category of obesity in the elderly. Nutrition, Metabolism, and Cardiovascular Diseases. 2008;**18**:388-395

[23] Piovezan RD, Hirotsu C, Moizinho R, de Sá Souza H, D'Almeida V, Tufik S, et al. Associations between sleep conditions and body composition states: Results of the EPISONO study. Journal of Cachexia, Sarcopenia and Muscle. 2019;**10**:962-973. DOI: 10.1002/jcsm.12445

[24] Roubenoff R, Roubenoff RA, Cannon JG, Kehayias JJ, Zhuang H, Dawson-Hughes B, et al. Rheumatoid cachexia: Cytokine-driven hypermetabolism accompanying reduced body cell mass in chronic inflammation. The Journal of Clinical Investigation. 1994;**93**:2379-2386. DOI: 10.1172/JCI117244

[25] Rajbhadary R, Khezri A, Panush RS. Rheumatoid cachexia: What is it and why is it important? The Journal of Rheumatology. 2011;**38**(3):406-408. DOI: 10.3899/jrheum.101036

[26] Roubenoff R. Rheumatoid cachexia: A complication of rheumatoid arthritis moves into the 21st century. Arthritis Research & Therapy. 2009;**11**:108

[27] Gregersen PK, Silver J, Winchester RJ. The shared epitope hypothesis: An approach to understanding the molecular genetics of susceptibility to rheumatoid arthritis. Arthritis & Rheumatology. 1987;**30**:1205-1213

[28] Mattey DL, Hassell AB, Dawes PT, et al. Independent association of rheumatoid factor and the HLA–DRB1 shared epitope with radiographic outcome in rheumatoid arthritis. Arthritis and Rheumatism. 2001;**44**:1529-1533

[29] Weyand CM, Hicok KC, Conn DL, et al. The influence of HLA–DRB1 genes on disease severity in rheumatoid arthritis. Annals of Internal Medicine. 1992;**117**:801-806

[30] Gonzalez-Gay MA, Hajeer AH, Dababneh A, et al. Sero-negative rheumatoid arthritis in elderly and polymyalgia rheumatica have similar patterns of HLA association. Journal of Rheumatology. 2001;**28**:122-125

[31] Kim EJ, Lee J, Ryu YS, et al. Shared epitope and radiologic progression are less prominent in elderly onset RA than young onset RA. Rheumatology International. 2013;**33**:2135-2140

[32] Hellier JP, Eliaou JF, Daur JP, et al. HLA-DRB1 genes and patients with late onset rheumatoid arthritis. Annals of the Rheumatic Diseases. 2001;**60**:531-533

[33] Wu H, Khanna D, Park G, et al. Interaction between RANKL and HLA-DRB1 genotypes may contribute to younger age at onset of seropositive rheumatoid arthritis in an inception cohort. Arthritis & Rheumatology. 2004;**50**:3093-3103

[34] Garatachea N, Lucía A. Genes and the ageing muscle: A review on genetic association studies. Age. 2013;**35**:207-233. DOI: 10.1007/s11357-011-9327-0

[35] Nishimura K et al. Meta-analysis: Diagnostic accuracy of anti-cyclic citrullinated peptide antibody and rheumatoid factor for rheumatoid arthritis. Annals of Internal Medicine. 2007;**146**:797-808

[36] Bizzaro N et al. Anti-cyclic citrullinated peptide antibody titer predicts time to rheumatoid arthritis onset in patients with undifferentiated arthritis: Results from a 2-year prospective study. Arthritis Research & Therapy. 2013;**15**:R16

[37] Malmstrom V, Catrina AI, Klareskog L. The immunopathogenesis of seropositive rheumatoid arthritis: From triggering to targeting. Nature Reviews. Immunology. 2017;**17**:60-75

[38] Padyukov L et al. A genome-wide association study suggests contrasting associations in ACPA-positive versus ACPA-negative rheumatoid arthritis. Annals of the Rheumatic Diseases. 2011;**70**:259-265

[39] Schuerwegh AJ et al. Evidence for a functional role of IgE anticitrullinated protein antibodies in rheumatoid arthritis. Proceedings of the National Academy of Sciences of the United States of America. 2010;**107**:2586-2591

[40] van Dongen H et al. Efficacy of methotrexate treatment in patients with probable rheumatoid arthritis: A double-blind, randomized, placebo-controlled trial. Arthritis and Rheumatism. 2007;**56**:1424-1432

[41] Sellam J et al. B cell activation biomarkers as predictive factors for the response to rituximab in rheumatoid arthritis: A six-month, national, multicenter, open-label study. Arthritis and Rheumatism. 2011;**63**:933-938

[42] Seegobin SD et al. ACPA-positive and ACPA-negative rheumatoid arthritis differ in their requirements for combination DMARDs and corticosteroids: Secondary analysis of a randomized controlled trial. Arthritis Research & Therapy. 2014;**16**:R13

[43] Raychaudhuri S et al. Five amino acids in three HLA proteins explain most of the association between MHC and seropositive rheumatoid arthritis. Nature Genetics. 2012;**44**:291-296

[44] Okada Y et al. Risk for ACPA-positive rheumatoid arthritis is driven by shared HLA amino acid polymorphisms in Asian and European populations. Human Molecular Genetics. 2014;**23**:6916-6926

[45] Mori M, Yamada R, Kobayashi K, Kawaida R, Yamamoto K. Ethnic differences in allele frequency of autoimmune-disease-associated SNPs. Journal of Human Genetics. 2005;**50**:264-266

[46] Healey LA. Subsets of rheumatoid arthritis in the aged. Arthritis & Rheumatology. 1986;**29**:149

[47] Healey LA, Sheets PK. The relation of polymyalgia rheumatica to rheumatoid arthritis. Journal of Rheumatology. 1988;**15**:750-752

[48] McCartey DJ, O'Duffy JD, Pearson L, et al. Remitting seronegative

symmetrical synovitis with pitting edema. JAMA. 1985;**254**:2763-2767

[49] Inoue K, Shichikawa K, Nishioka J, et al. Older age onset rheumatoid arthritis with or without osteoarthritis. Annals of the Rheumatic Diseases. 1987;**46**:908-911

[50] Goemaere S, Ackerman C, Goethals K, et al. Onset of symptoms of rheumatoid arthritis in relation to age, sex and menopausal transition. Journal of Rheumatology. 1990;**17**:1620-1622

[51] Ferraccioli GF, Cavalieri F, Mercandati M, et al. Clinical features, scintiscan characteristics and X-ray progression of late onset rheumatoid arthritis. Clinical and Experimental Rheumatology. 1984;**2**:157-161

[52] Türkçapar N, Demir O, Atli T, et al. Late onset rheumatoid arthritis: Clinical and laboratory comparisons with younger onset patients. Archives of Gerontology and Geriatrics. 2006;**42**:225-231

[53] van der Heijde DM, van Riel PL, van Leeuwen MA, et al. Older versus younger onset rheumatoid arthritis: Results at onset and after 2 years of a prospective follow-up study of early rheumatoid arthritis. Journal of Rheumatology. 1991;**18**:1285-1289

[54] Lance NJ, Curran JJ. Late-onset, seropositive, erosive rheumatoid arthritis. Seminars in Arthritis and Rheumatism. 1993;**23**:177-182

[55] Lin JZ, Liang JJ, Ma JD, Li QH, Mo YQ, Cheng WM, et al. Myopenia is associated with joint damage in rheumatoid arthritis: A cross-sectional study. Journal of Cachexia, Sarcopenia and Muscle. 2019;**10**:355-367. DOI: 10.1002/jcsm.12381

[56] Chen CT, Lin JZ, Ma JD, Li QH, Mo YQ, Chen LF, et al. Myopenia in elderly female patients with rheumatoid arthritis is associated with severe joint damage: A cross-sectional study. In: 2019 ACR/ARP Annual Meeting Abstract 475

[57] van Schaardenburg D, Hazes JM, de Boer A, et al. Outcome of rheumatoid arthritis in relation to age and rheumatoid factor at diagnosis. Journal of Rheumatology. 1993;**20**:45-52

[58] Cho SK, Sung YK, Choi CB, et al. Do patients with elderly-onset rheumatoid arthritis have severe functional disability? Seminars in Arthritis and Rheumatism. 2012;**42**:23-31

[59] Chen DY, Hsieh TY, Chen YM, et al. Proinflammatory cytokine profiles of patients with elderly-onset rheumatoid arthritis: A comparison with younger-onset disease. Gerontology. 2009;**55**:250-258

[60] Pease CT, Bhakta BB, Devlin J, et al. Does the age of onset of rheumatoid arthritis influence phenotype? A prospective study of outcome and prognostic factors. Rheumatology (Oxford). 1999;**38**:228-234

[61] Calvo-Alen J, Corrales A, Sanchez-Andrada S, et al. Outcome of late-onset rheumatoid arthritis. Clinical Rheumatology. 2005;**24**:485-489

[62] Krams T, Ruyssen-Witrand A, Nigon D, et al. Effect of age at rheumatoid arthritis onset on clinical, radiographic, and functional outcomes: The ESPOIR cohort. Joint, Bone, Spine. 2016;**83**:511-515

[63] Wabe N, Wiese MD. Treating rheumatoid arthritis to target: Physician and patient adherence issues in contemporary rheumatoid arthritis therapy. Journal of Evaluation in Clinical Practice. 2017;**23**:486-493

[64] Aletah D, Smolen JS. Diagnosis and management of rheumatoid arthritis: A review. JAMA. 2018;**320**(13)

[65] Metsios GS, Stavropoulos-Kalinoglou A, Veldhuijzen van Zanten JJCS, Treharne GJ, Panoulas VF, Douglas KMJ, et al. Rheumatoid arthritis, cardiovascular disease and physical exercise: A systematic review. Rheumatology. 2008;**47**:239-248. DOI: 10.1093/rheumatology/kem260

[66] Lee DM, Weinblatt ME. Rheumatoid arthritis. Lancet. 2001;**358**:903-911

[67] Ekdahl C, Broman G. Muscle strength, endurance, and aerobic capacity in rheumatoid arthritis: A comparative study with healthy subjects. Annals of the Rheumatic Diseases. 1992;**51**:35-40

[68] de Jong Z, Munneke M, Zwinderman AH, et al. Is a long-term high-intensity exercise program effective and safe in patients with rheumatoid arthritis? Results of a randomized controlled trial. Arthritis and Rheumatism. 2003;**48**:2415-2424

[69] Hakkinen A. Effectiveness and safety of strength training in rheumatoid arthritis. Current Opinion in Rheumatology. 2004;**16**:132-137

[70] Cooney JK, Law R-J, Matschke V, Lemmey AB, Moore JP, Ahmad Y, et al. Benefits of exercise in rheumatoid arthritis. Journal of Aging Research. 2011; Article ID 681640, 14 p. DOI: 10.4061/2011/681640

[71] Al-Qubaeissy KY, Fatoye FA, Goodwin PC, et al. The effectiveness of hydrotherapy in the Management of Rheumatoid Arthritis: A systematic review Musculoskelet. Care. 2013;**11**:3-18

[72] Fried LP, Ferrucci L, Darer J, Williamson JD, Anderson G. Untangling the concepts of disability, frailty, and comorbidity: Implications for improved targeting and care. The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences. 2004;**59**:25563

[73] Espinoza SE, Fried LP. Risk factors for frailty in the older adult. Clinical Geriatrics. 2007;**15**:37-44

[74] Yao X, Li H, Leng SX. Inflammation and immune system alterations in frailty. Clinics in Geriatric Medicine. 2011;**27**:79-87

[75] Dent E, Kowal P, Hoogendijk EO. Frailty measurement in research and clinical practice: A review. European Journal of Internal Medicine. 2016;**31**:3-10

[76] De Vries NM, Staal JB, van Ravensberg CD, Hobbelen JS, Olde Rikkert MG, Nijhuis-van Der Sanden MW. Outcome instruments to measure frailty: A systematic review. Ageing Research Reviews. 2011;**10**:104-114

[77] Haider S, Grabovac I, Berner C, Lamprecht T, Fenzl K-H, Erlacher L, et al. Frailty in seropositive rheumatoid arthritis patients of working age: A cross-sectional. Clinical and Experimental Rheumatology. 2019;**37**:585-592

[78] Armstrong EJ, Harskamp CT, Armstrong AW. Psoriasis and major adverse cardiovascular events: A systematic review and meta-analysis of observational studies. Journal of the American Heart Association. 2013;**2**:e000062. DOI: 10.1161/JAHA.113.000062

[79] Avina-Zubieta JA, Thomas J, Sadatsafavi M, Lehman AJ, Lacaille D. Risk of incident cardiovascular events in patients with rheumatoid arthritis: A meta-analysis of observational studies.

Annals of the Rheumatic Diseases. 2012;**71**:1524-1529

[80] Filimon AM, Negreanu L, Doca M, Ciobanu A, Preda CM, Vinereanu D. Cardiovascular involvement in inflammatory bowel disease: Dangerous liaisons. World Journal of Gastroenterology. 2015;**21**:9688-9692

[81] Soubrier M, Barber Chamoux N, Tatar Z, Couderc M, Dubost JJ, Mathieu S. Cardiovascular risk in rheumatoid arthritis. Joint, Bone, Spine. 2014;**81**:298-302

[82] Ahlehoff O, Gislason GH, Charlot M, Jorgensen CH, Lindhardsen J, Olesen JB, et al. Psoriasis is associated with clinically significant cardiovascular risk: A Danish nationwide cohort study. Journal of Internal Medicine. 2011;**270**:147-157

[83] Brady SR, de Courten B, Reid CM, Cicuttini FM, de Courten MP, Liew D. The role of traditional cardiovascular risk factors among patients with rheumatoid arthritis. The Journal of Rheumatology. 2009;**36**:34-40

[84] Lindhardsen J, Ahlehoff O, Gislason GH, Madsen OR, Olesen JB, Torp-Pedersen C, et al. The risk of myocardial infarction in rheumatoid arthritis and diabetes mellitus: A Danish nationwide cohort study. Annals of the Rheumatic Diseases. 2011;**70**(6):929-934. DOI: 10.1136/ard.2010.143396

[85] Peters MJ, van Halm VP, Voskuyl AE, Smulders YM, Boers M, Lems WF, et al. Does rheumatoid arthritis equal diabetes mellitus as an independent risk factor for cardiovascular disease? A prospective study. Arthritis and Rheumatism. 2009;**61**:1571-1579

[86] del Rincon I, Polak JF, O'Leary DH, Battafarano DF, Erikson JM, Restrepo JF, et al. Systemic inflammation and cardiovascular risk factors predict rapid progression of atherosclerosis in rheumatoid arthritis. Annals of the Rheumatic Diseases. 2015;**74**:1118-1123

[87] Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Borden WB. Heart disease and stroke statistics—2013 update: A report from the American Heart Association. Circulation. 2013;**127**:e6-e245

[88] Kalogeropoulos A, Georgiopoulou V, Psaty BM, Rodondi N, Smith AL, Harrison DG, et al. Inflammatory markers and incident heart failure risk in older adults: The health ABC (health, aging, and body composition) study. Journal of the American College of Cardiology. 2010;**55**:2129-2137

[89] Aslam F, Bandeali SJ, Khan NA, Alam M. Diastolic dysfunction in rheumatoid arthritis: A meta-analysis and systematic review. Arthritis Care and Research. 2013;**65**:534-543

[90] Cioffi G, Viapiana O, Ognibeni F, Dalbeni A, Giollo A, Gatti D, et al. Prognostic role of subclinical left ventricular systolic dysfunction evaluated by speckle-tracking echocardiography in rheumatoid arthritis. Journal of the American Society of Echocardiography. 2017;**30**:602-611

[91] Foster W, Carruthers D, Lip GY, Blann AD. Inflammation and microvascular and macrovascular endothelial dysfunction in rheumatoid arthritis: Effect of treatment. The Journal of Rheumatology. 2010;**37**:711-716

[92] Marti CN, Gheorghiade M, Kalogeropoulos AP, Georgiopoulou VV, Quyyumi AA, Butler J. Endothelial dysfunction, arterial stiffness, and heart failure. Journal of the American College of Cardiology. 2012;**60**:1455-1469

[93] Midtbo H, Semb AG, Matre K, Kvien TK, Gerdts E. Disease activity is associated with reduced left ventricular systolic myocardial function in patients with rheumatoid arthritis. Annals of the Rheumatic Diseases. 2017;**76**:371-376

[94] 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. Journal of the American College of Cardiology. 2013;**62**:263-271

[95] Fan F, Galvin A, Fang L, White DA, Moore XL, Sparrow M, et al. Comparison of inflammation, arterial stiffness and traditional cardiovascular risk factors between rheumatoid arthritis and inflammatory bowel disease. Journal of Inflammation (London). 2014;**11**:29

[96] Mantel A, Holmqvist M, Andersson DC, Lund LH, Askling J. Association between rheumatoid arthritis and risk of ischemic and nonischemic heart failure. Journal of the American College of Cardiology. 2017;**69**:1275-1285

[97] Nicola PJ, Maradit-Kremers H, Roger VL, Jacobsen SJ, Crowson CS, Ballman KV, et al. The risk of congestive heart failure in rheumatoid arthritis: A population-based study over 46 years. Arthritis and Rheumatism. 2005;**52**:412-420

[98] Khalid U, Egeberg A, Ahlehoff O, Lane D, Gislason GH, Lip GYH, et al. Incident heart failure in patients with rheumatoid arthritis: A nationwide cohort study. Journal of the American Heart Association. 2018;**7**:e007227. DOI: 10.1161/JAHA.117.007227

[99] Avouac J, Meune C, Chenevier-Gobeaux C, Dieude P, Borderie D, Lefevre G, et al. Inflammation and disease activity are associated with high circulating cardiac markers in rheumatoid arthritis independently of traditional cardiovascular risk factors. The Journal of Rheumatology. 2014;**41**:248-255

[100] Masoud S, Lim PB, Kitas GD, Panoulas V. Sudden cardiac death in patients with rheumatoid arthritis. World Journal of Cardiology. 2017;**9**(7):562-573

[101] Peters MJ, Symmons DP, McCarey D, Dijkmans BA, Nicola P, Kvien TK, et al. EULAR evidence-based recommendations for cardiovascular risk management in patients with rheumatoid arthritis and other forms of inflammatory arthritis. Annals of the Rheumatic Diseases. 2010;**69**:325-331. DOI: 10.1136/ard.2009.113696

[102] Deane KD. Can rheumatoid arthritis be prevented? Best Practice & Research. Clinical Rheumatology. 2013;**27**:467-485

[103] Finckh A, Liang MH, van Herckenrode CM, de Pablo P. Long-term impact of early treatment on radiographic progression in rheumatoid arthritis: A metaanalysis. Arthritis and Rheumatism. 2006;**55**:864-872

[104] Fuchs HA, Kaye JJ, Callahan LF, Nance EP, Pincus T. Evidence of significant radiographic damage in rheumatoid arthritis within the first 2 years of disease. The Journal of Rheumatology. 1989;**16**:585-591

[105] Cohen S, Emery P. The American College of Rheumatology/European League Against Rheumatism criteria for the classification of rheumatoid arthritis: A game changer. Arthritis and Rheumatism. 2010;**62**:2592-2594

[106] Guo X, Wang Y, Xu D, Nossent J, Pavlos NJ, Xu J. Rheumatoid arthritis: Pathological mechanisms and modern pharmacologic therapies. Bone

Research. 2018;**6**:15. DOI: 10.1038/s41413-018-0016-9

[107] Studenski SA, Ward MM. Pharmacology and the elderly. In: Harris ED Jr, Budd RC, Firestein GS, et al., editors. Kelley's Textbook of Rheumatology. 7th ed. Philadelphia, PA: Elsevier Saunders; 2005. pp. 961-966

[108] Walker J, Wynne H. The frequency and severity of adverse drug reactions in older people. Age and Ageing. 1994;**23**:255-259

[109] Tutuncu Z, Reed G, Kremer J, et al. Do patients with older-onset rheumatoid arthritis receive less aggressive treatment? Annals of the Rheumatic Diseases. 2006;**65**:1226-1229

[110] Innala L, Berglin E, Moler B, et al. Age at onset determines severity and choice of treatment in early rheumatoid arthritis: A prospective study. Arthritis Research & Therapy. 2014;**16**:R94

[111] Mueller RB, Reshiti N, Kaegi T, et al. Does addition of glucocorticoids to the initial therapy influence the later course of the disease in patients with early RA? Results from the Swiss prospective observational registry (SCQM). Clinical Rheumatology. 2017;**36**:59-66

[112] Genevay S, Finckh A, Ciurea A, et al. Tolerance and effectiveness of anti-tumor necrosis-alpha therapies in elderly patients with rheumatoid arthritis: A population based cohort study. Arthritis and Rheumatism. 2007;**57**:679-685

[113] Bathon JM, Fleischmann RM, Van der Heijde D, et al. Safety and efficacy of etanercept treatment in elderly subjects with rheumatoid arthritis. The Journal of Rheumatology. 2006;**33**:234-243

[114] Pers YM, Schaub R, Constant E, et al. Efficacy and safety of tocilizumab in elderly patients with rheumatoid arthritis. Joint, Bone, Spine. 2015;**82**:25-30

[115] Curtis JR, Schulze-Koops H, Takiya L, et al. Efficacy and safety of tofacitinib in older and younger patients with rheumatoid arthritis. Annals of the Rheumatic Diseases. 2013;**65** (Suppl 10):2331

[116] Kobak S, Bes C. An autumn tale: Geriatric rheumatoid arthritis. Therapeutic Advances in Musculoskeletal Disease. 2018;**10**(1):3-11