Review

Sarcopenia in autoimmune and rheumatic diseases:

a comprehensive review

Hyo Jin An1, Kalthoum Tizaoui2, Salvatore Terrazzino3, Sarah Cargnin3, Keum Hwa Lee4, Seoung Wan Nam5, Jae Seok Kim6, Jae Won Yang6, Jun Young Lee6, Lee Smith7, Ai Koyanagi8,9, Louis Jacob8,10, Han Li11, Jae Il Shin4,\* and Andreas Kronbichler12

1 Yonsei University College of Medicine, Seoul, Republic of Korea; hjj622@yonsei.ac.kr

2 Department of Basic Sciences, Division of Histology and Immunology, Faculty of Medicine Tunis, Tunis El Manar University, Tunis 1068, Tunisia; kalttizaoui@gmail.com

3 Department of Pharmaceutical Sciences and Interdepartmental Research Center of Pharmacogenetics and Pharmacogenomics (CRIFF), University of Piemonte Orientale, Novara, Italy; salvatore.terrazzino@uniupo.it (S.T.); sarah.cargnin@uniupo.it (S.C.)

4 Department of Pediatrics, Yonsei University College of Medicine, Seoul, Republic of Korea; AZSAGM@yuhs.ac (K.H.L.); SHINJI@yuhs.ac (J.I.S.)

5 Department of Rheumatology, Wonju Severance Christian Hospital, Yonsei University Wonju College of Medicine, Wonju, Korea; dahsome@gmail.com

6 Department of Nephrology, Yonsei University Wonju College of Medicine, Wonju, Republic of Korea; ripplesong@yonsei.ac.kr (J.S.K.); kidney74@yonsei.ac.kr (J.W.Y.); junyoung07@yonsei.ac.kr (J.Y.L.)

7 The Cambridge Centre for Sport and Exercise Science, Anglia Ruskin University, Cambridge, CB1 1PT, UK; Lee.Smith@anglia.ac.uk

8 Research and Development Unit, Parc Sanitari Sant Joan de Déu, CIBERSAM, 08830 Barcelona, Spain; a.koyanagi@pssjd.org (A.K.); louis.jacob.contacts@gmail.com (L.J.)

9 ICREA, Pg. Lluis Companys 23, 08010 Barcelona, Spain

10 Faculty of Medicine, University of Versailles Saint-Quentin-en-Yvelines, 78000 Versailles, France

11 University of Florida College of Medicine, Gainesville FL 32601, USA; lih2@ufl.edu

12 Department of Internal Medicine IV (Nephrology and Hypertension), Medical University Innsbruck, Innsbruck, Austria; Andreas.Kronbichler@i-med.ac.at

**\*** Correspondence: SHINJI@yuhs.ac; Tel.: +82-2-2228-2050

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**Abstract:** Sarcopenia refers to a decrease in skeletal muscle mass and function. As sarcopenia affects mortality, and causes significant disability, the clinical importance of sarcopenia is emerging. Sarcopenia has been recognized as an age-related disease at first but recently it has been reported to be prevalent also in younger patients with autoimmune disease. Specifically, the association of sarcopenia and autoimmune diseases such as rheumatoid arthritis has been studied in detail. Although the pathogenesis of sarcopenia in autoimmune disease has not been elucidated, chronic inflammation is believed to contribute to sarcopenia, and moreover the pathogenesis seems to be different depending on the respective underlying disease. The definition of sarcopenia differs between studies, which limits direct comparisons. Thus, in this review, we cover various definitions of sarcopenia used in previous studies and highlight the prevalence of sarcopenia in diverse autoimmune diseases including rheumatoid arthritis, spondyloarthritis, systemic sclerosis, inflammatory bowel disease, and autoimmune diabetes. In addition, we cover the pathogenesis and treatment of sarcopenia in autoimmune and rheumatic diseases. This review provides a comprehensive understanding of sarcopenia in various autoimmune diseases and highlights the need for a consistent definition of sarcopenia.

**Keywords:** Sarcopenia; Rheumatic disease; Autoimmune disease; Rheumatoid arthritis; Inflammatory bowel disease; Type 1 diabetes

1. Introduction

The loss of muscle mass and function with aging is a natural phenomenon. In the seventh and eighth decade of life, muscle strength decrease by 20-40% and the degree of reduction increases gradually [1]. Decrease in skeletal muscle mass, strength and function associated with aging is termed sarcopenia [2–4]. Sarcopenia is associated with daily life disability, falls in older people, and a high risk of all-cause mortality [5,6]. Furthermore, it is associated with financial burden because the hospitalization costs for patients with sarcopenia are significantly higher than those without [7]. As the clinical importance of sarcopenia has become apparent, it is now considered a disease entity in the International Classification of Diseases (ICD) [8]. Whereas sarcopenia is usually considered an age-related disorder, younger people with various clinical conditions also suffer from sarcopenia. Age-related sarcopenia with no other causes is called ‘primary sarcopenia’ while when one or more other causes such as malnutrition are evident, sarcopenia can be classified as ‘secondary sarcopenia’ [4]. In many cases, sarcopenia is not only age-related but also is a multi-factorial problem [9]. It is well known that endocrine diseases or malignancies promote sarcopenia [10]. Likewise, chronic inflammation is also a paramount risk factor for sarcopenia [10,11]. From this point of view, autoimmune diseases with persistent chronic inflammation due to autoreactive immune response, might be a risk factor for sarcopenia. Indeed, a recent study showed that having any autoimmune disease was associated with sarcopenia with an odds ratio (OR) of 1.83 [12]. In addition, the association between rheumatoid arthritis (RA) and sarcopenia is well established. Nevertheless, to date, there are no comprehensive reviews regarding the relationship of sarcopenia and autoimmune diseases. This review addresses this gap and covers the association between sarcopenia and autoimmune or rheumatic diseases. This review mainly addresses RA than other diseases due to a difference in the sufficiency of studies.

2. Definition and diagnosis of sarcopenia

In 1989, Irwin Rosenberg first coined the term ‘sarcopenia’ (Greek ‘sarx’ or flesh + ‘penia’ or loss) to define the decrease of skeletal muscle mass but until now there is no unified definition or diagnosis of sarcopenia [2,3]. Baumgartner et al. defined sarcopenia by skeletal muscle mass [13]. Skeletal muscle mass index (SMI) was defined as appendicular skeletal muscle mass (ASM)/height2 (kg/m2), and sarcopenia was defined if SMI was two standard deviation below the mean of a gender-specific reference group [13]. After a few years, Janssen et al. proposed cut points of height-adjusted skeletal muscle mass that were associated with a physical disability risk [14]. Afterward, several consensus groups proposed the definition using both muscle mass and function [4,15–18]. In 2010, the European Working Group on Sarcopenia in Older People (EWGSOP), stated sarcopenia as ‘a syndrome characterized by progressive and generalized loss of skeletal muscle mass and strength with a risk of adverse outcomes such as physical disability, poor quality of life and death’, a definition that now represents the most widely used in the clinical realm [4]. According to EWGSOP, the definition of sarcopenia was (1) having low muscle mass plus (2) having low muscle strength or low physical performance [4]. The Foundation of the National Institute of Health (FNIH) [15], the International Working Group on Sarcopenia (IWGS) [16] and the European Society on Clinician Nutrition and Metabolism special interest groups (ESPEN SIG) [17] also proposed a definition of sarcopenia containing both muscle mass and function. The Asian Working Group for Sarcopenia (AWGS) took a similar approach for sarcopenia but proposed a new and more appropriate cutoff value for Asians, considering that already proposed cutpoints were calculated from Caucasian data [18]. Recently, the European Working Group on Sarcopenia in Older People 2 (EWGSOP2) revised the definition of sarcopenia which is characterized by (1) low muscle strength and (2) low muscle quantity or quality [19]. This change reflected the study results that muscle strength is a more important prognostic factor than muscle mass [20–23].

3. Epidemiology of sarcopenia in autoimmune and rheumatic disease patients

Table 1 shows the prevalence of sarcopenia inautoimmune and rheumatic diseases. The prevalence of sarcopenia varies not only on the type of autoimmune disease, but also the different definitions used and the subject groups analyzed. Overall, the clinical definition was heterogeneous. Many studies have defined sarcopenia using only one aspect with muscle mass or lean mass, which are calculated by SMI or free fat mass index (FFMI) respectively. On the other hand, other studies have defined it by muscle mass plus muscle strength (e.g. handgrip strength) or performance (e.g. TUG; timed up and go). Furthermore, the cut-off value for sarcopenia differed between studies. The column ‘definition of sarcopenia’ highlights the respective criteria used to define sarcopenia. Krajewska-Włodarczyk et al. demonstrated that the difference in definition affects the study results [24]. In female patients with psoriatic arthritis (PsA), the prevalence of sarcopenia was 13.7, 48.0 and 43.1% respectively when diagnosed by different definition of SMI; (1) appendicular muscle mass/height2 <5.45kg/m2 [13], (2) skeletal muscle mass/weight x100 <27.6% [25], (3) skeletal muscle mass/weight x100 <27.6% with TUG>14s [25]. The heterogeneity of prevalence due to different definition of sarcopenia urges the need for a unified definition and diagnostic criteria for sarcopenia.

3.1. Rheumatoid arthritis

Among the studies investigating the prevalence of sarcopenia in autoimmune diseases, most studies were performed in RA patients. Dao et al. [26], Santos et al. [27], Giles et al. [28], Doğan et al. [29], Tournadre et al. [30] and Lin et al. [31] performed cross-sectional studies, and revealed that the overall prevalence of sarcopenia is significantly higher in RA compared to controls. In twelve RA studies as highlighted in Table 1, the prevalence of sarcopenia ranges from 10.1 to 45.1% and the median value is 29.1% [26–37]. There are significant gaps among the figures. The gap seems to result from the diversity in definition of sarcopenia and the different features of each group such as drug use, disease activity, and ethnicity. In conclusion, RA patients are susceptible to sarcopenia but it is difficult to determine the exact prevalence of sarcopenia in RA from those studies due to their heterogeneity.

3.2. Spondyloarthritis

We found three valid studies concerning the prevalence of sarcopenia in Spondyloarthritis (SpA). Barone et al. studied Caucasian SpA patients aged between 40 and 75 years excluding those with obesity; 22 with ankylosing spondylitis (AS) and 70 with PsA [33]. The prevalence of sarcopenia diagnosed by SMI and handgrip strength was 22.7% in AS, and 20.0% in PsA [33]. The difference in the prevalence of sarcopenia between RA, PsA and AS was not significant, whereas the prevalence of pre-sarcopenia (decreased muscle mass without reduced strength) was significantly different (As>PsA>RA) in the study [33]. In male Moroccan AS patients, the prevalence of sarcopenia was 34.3% according to the definition of EWGSOP [38]. In another study, female patients with PsA from Poland with an age range of 50 to 75 years, the prevalence of sarcopenia was 13.7, 48.0, and 43.1% each for different definitions [24].

3.3. Systemic lupus erythematosus

In the study by Santos et al., 16 out of 92 participants (17.4%) with a diagnosis of systemic lupus erythematosus (SLE) were sarcopenic [27]. Among them, 10.9% of patients were sarcopenic but not obese, and 6.5% patients were both sarcopenic and obese. Both numbers were significantly higher than the controls (purely sarcopenic; p=0.01, sarcopenic obesity; p=0.009).

3.4. Systemic sclerosis

Three studies calculated the prevalence of sarcopenia in Systemic sclerosis (SSc). The prevalence was 20.7% when defining sarcopenia using SMI [39] and 22.5% in a study from Germany, which included 91.5% females and followed the definition of EWGSOP [4,40]. Another study reported higher prevalence rates of 41.9 and 54.8% applying SMI and handgrip strength criteria, respectively [41].

3.5. Inflammatory bowel disease

To estimate the degree of sarcopenia in inflammatory bowel disease (IBD), a few studies used lumbar SMI assessed by computed tomography (CT) scan, dual-energy X-ray absorptiometry (DXA) or bioelectrical impedance analysis (BIA). Zhang et al. observed that sarcopenia was more prevalent in ulcerative colitis (UC) and Crohn’s disease (CD) compared to controls (all p<0.05) [42]. Among patients with IBD, the prevalence of sarcopenia was significantly higher in CD patients (p<0.05) [42]. The prevalence of sarcopenia in UC ranged from 14.8 to 69.5% [42–46]. The studies used lumbar SMI to define sarcopenia with different cut-off points. The reason for this large gap seems to result from the difference of respective inclusion criteria of the subjects. The highest prevalence of 69.5% was measured in patients who were hospitalized due to acute severe UC [43], and the lowest was in newly diagnosed patients with an age under 13 years [44]. In CD, the prevalence of sarcopenia was higher than in other autoimmune diseases. It ranges between 31.0 and 61.4% and the median was 40.2% [42,44–52]. The numbers might be overestimated due to two reasons. First, the subject groups were also skewed as described above for UC. One point is that in general, CT data, which was used to diagnose sarcopenia, is scarce in stable patients. Therefore, subjects undergoing surgery after the CT scan were included to propose the frequency of sarcopenia [47,48], or hospitalized due to disease exacerbation [45], or suspected complications of CD [49]. Second, there could be an overlap between the two studies showing the highest prevalence because the data were measured in an identical hospital in a similar time period [42,47].

3.6. Other autoimmune diseases

The prevalence of sarcopenia in type 1 diabetes mellitus (T1DM) and latent autoimmune diabetes in adults (LADA) patients was 16.6 and 35.0% respectively [53,54]. The subjects were Japanese, and sarcopenia was diagnosed according to AWGS. In LADA, the prevalence was significantly higher than in controls [54]. Among Canadian autoimmune liver disease patients who were evaluated for liver transplantation, 41.8% of the patients were sarcopenic as diagnosed by SMI [55].

**Table 1.** Prevalence of sarcopenia in patients with autoimmune and rheumatic diseases.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Author** | **Prevalence (%)** | | **Patients (N)** | **Group Feature** | **P-value** | **Definition of Sarcopenia**  **(Cutoff)** |
| **Rheumatoid arthritis** | | | | | | |
| Dao et al. [26] 1 | Purely sarcopenic | 18.1 | 105 | Vietnamese, female | 0.007 | FFMI (Hull et al. [56]) |
| Sarcopenic obesity2 | 12.4 | 0.002 |
| Total | 30.5 | - |
| Santos et al. [27] 1 | Purely sarcopenic | 4.5 | 89 | Caucasian, Portuguese, female | >0.053 | FFMI (Schutz et al. [57]) |
| Sarcopenic obesity2 | 5.6 | 0.01 |
| Total | 10.1 | - |
| Giles et al. [28] | Male | 33.3 | 72 | American | 0.1573 | SMI (Janssen et al. [14]) |
| Female | 21.4 | 117 | 0.004 |
| Total | 25.9 | 189 | - |
| Doğan et al. [29] | 43.3 | | 30 | Female,  Age: 35–50 | 0.004 | SMI (Janssen et al. [14]) |
| Tournadre et al. [30] | 28.6 | | 21 | Active RA  (DAS28>3.2) | <0.05 | SMI (Baumgartner et al. [13]) |
| Lin et al. [31] | 45.1 | | 457 | Chinese | <0.054 | SMI (AWGS [18]) |
| Ngeuleu et al. [34] | 39.8 | | 123 | Moroccan | - | SMI (Baumgartner et al. [13]) |
| Tada et al. [35] | 28.0 | | 100 | Japanese | - | AWGS [18] |
| Mochizuki et al. [36] | 29.6 | | 240 | Japanese,  age ≥65 | - | AWGS[18] |
| Torii et al. [37] | 37.1 | | 388 | Japanese, female | - | EWGSOP [4], AWGS[18] |
| Vlietstra et al. [32] | 17.1 | | 82 | New Zealander | - | SMI (FNIH[15]) |
| Barone et al. [33] | 21.0 | | 76 | Caucasian, Italian, age: 40-75 | - | SMI (Janssen et al. [14]),  HS (Lauretani et al. [58]) |
| **Spondyloarthritis**  **Ankylosing spondylitis** | | | | | | |
| Barone et al. [33] | 22.7 | | 22 | Caucasian, Italian, age: 40-75 | - | SMI (Janssen et al. [14]),  HS (Lauretani et al. [58]) |
| El Maghraoui et al. [38] | 34.3 | | 67 | Moroccan, male | - | EWGSOP [4] |
| **Psoriatic arthritis** | | | | | | |
| Barone et al. [33] | 20.0 | | 70 | Caucasian, Italian, age: 40-75 | - | SMI (Janssen et al. [14]),  HS (Lauretani et al. [58]) |
| Krajewska-Włodarczyk et al. [24] | 13.7 | | 51 | Polish, age: 50-75, female | - | SMI (Baumgartner et al. [13]) |
| 48.0 | | SMI (Janssen et al. [25]) |
| 43.1 | | SMI(Janssen et al. [25]),  TUG>14s |
| **Systemic lupus erythematosus** | | | | | | |
| Santos et al. [27] 1 | Purely sarcopenic | 10.9 | 92 | Caucasian, Portuguese, female | 0.01 | FFMI (Schutz et al. [57]) |
| Sarcopenic obesity2 | 6.5 | 0.009 |
| Total | 17.4 | - |
| **Systemic sclerosis** | | | | | | |
| Caimmi et al. [39] | 20.7 | | 140 | Italian | - | SMI (Baumgartner et al. [13]) |
| Siegert et al. [40] | 22.5 | | 129 | German, 91.5% female | - | EWGSOP [4] |
| Corallo et al. [41] | 41.9 | | 62 | Caucasian, Italian | - | SMI (Baumgartner et al. [13]) |
| 54.8 | | HS  (Male: <30, Female:<20) |
| **Inflammatory bowel disease**  **Ulcerative colitis** | | | | | | |
| Zhang et al. [42] | 27.3 | | 99 | Chinese. | <0.05 | SMI (Fearon et al. [59]) |
| Cushing et al. [43] | 69.5 | | 82 | Admitted for ASUC | - | SMI (Fearon et al. [59]) |
| Mager et al. [44] | 14.8 | | 27 | Age: 5-18 | - | SMM z score<-2 [60] |
| Bamba et al. [45] | 48.3 | | 29 | Japanese | - | SMI (Nishikawa et al. [61]) |
| Adams et al. [46] | 53.8 | | 13 | American | - | SMI (Prado et al. [62]) |
| **Crohn’s disease** | | | | | | |
| Zhang et al. [42] | 59.0 | | 105 | Chinese | <0.05 | SMI (Fearon et al. [59]) |
| Mager et al. [44] | 31.0 | | 58 | Age: 5-18 | - | SMM z score<-2 [60] |
| Zhang et al. [47] | 61.4 | | 114 | Chinese, required BR | - | SMI (Fearon et al. [59]) |
| O'Brien et al. [48] | 39.0 | | 77 | Retrospectively selected (BR) | - | SMI (Martin et al. [63]) |
| Bamba et al. [45] | 37.2 | | 43 | Japanese | - | SMI (Nishikawa et al. [61]) |
| Thiberge et al. [49] | 33.6 | | 149 | French | - | SMI (Mourtzakis et al. [64]) |
| Adams et al. [46] | 44.2 | | 77 | American | - | SMI (Prado et al. [62]) |
| Lee et al. [50] | 50.6 | | 79 | Korean | - | SMI (Kim et al. [65]) |
| Cravo et al. [51] | 31.0 | | 71 | Portuguese | - | SMI (Martin et al. [63]) |
| Carvalho et al. [52] | 41.4 | | 58 | Portuguese | - | SMI (Prado et al. [62]) |
| **Diabetes**  **Type 1 diabetes mellitus** | | | | | | |
| Mori et al. [53] | 16.6 | | 36 | Japanese | - | AWGS [18] |
| **Latent autoimmune diabetes in adults** | | | | | | |
| Bouchi et al. [54] | 35.0 | | 20 | Japanese | 0.022 | AWGS [18] |
| **Autoimmune liver disease**  **(Autoimmune hepatitis, Primary biliary cirrhosis, primary sclerosing cholangitis)** | | | | | | |
| Montano-Loza et al. [55] | 41.8 | | 55 | Canadian, evaluated for LT | - | SMI (Martin et al. [63]) |

FFMI, Free fat mass index; SMI, Skeletal muscle mass index; RA, rheumatoid arthritis; DAS28, disease activity score in 28 joints; HS, handgrip strength; TUG, timed up and go; ASUC, acute severe ulcerative colitis; SMM, skeletal muscle mass; BR, bowel resection; LT, liver transplantation.

1 Sarcopenia was divided into two groups; purely sarcopenic, sarcopenic obesity

2 Sarcopenic obesity refers to a medical condition that the loss of muscle is accompanied by increased fat mass.

3 Not statistically significant

4 P-value was measured respectively according to sex and age. Each p-value was <0.05

4. Rheumatoid arthritis and sarcopenia

RA is a chronic inflammatory autoimmune disease that affects multiple synovial joints. Sarcopenia is a frequent comorbidity of RA that occurs in 10.1-45.1% of patients (Table 1). Occasionally, loss of muscle is accompanied by increased fat mass which is called sarcopenic obesity. Rheumatoid cachexia is a more serious condition and refers to the state of exhaustion and loss of overall body composition, including muscle and fat [66]. It is also a common condition in RA with a prevalence of 15-32% [67]. Many studies supported the idea that RA patients have lower skeletal muscle mass resulting in a higher prevalence of sarcopenia compared to those without RA [26,29,68,69]. As shown in Table 2, sarcopenia in RA is clinically meaningful, since it is associated with the incidence of low bone mineral density, falls and fractures [36,37]. In addition, sarcopenic RA patients have endothelial dysfunction and a higher cardiometabolic risk [34,70]. Health Assessment Questionnaire Disability Index (HAQ-DI) is the measure to assess the functional ability of chronic illness patients, especially RA [71]. Several studies have reported that high HAQ-DI scores are well associated with sarcopenia in RA [28,31,72,73].

4.1. Associated factors

The factors associated with sarcopenia in RA have been demonstrated in many studies (Table 2). Old age [36,37], BMI [34–36], high body fat mass [32,35], longer disease duration [37,74], bone erosion [34], low hip bone mineral density [36], malnutrition [37], low protein intake [72], and joint damage [28,31,37] were all associated with sarcopenia. Acute phase reactants such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) [28,36,68,72], rheumatoid factor (RF) [26,28], and matrix metalloprotease 3 (MMP3) [35] were also associated. On the other hand, conflicting results have been found for other factors. Disease activity, which was measured by the disease activity score in 28 joints (DAS28), was associated with abnormal body composition in one study [26], while others did not find a significant association [28,32,34,35]. Tada et al. stated that no significant correlation between sarcopenia and RA activity in the study might be due to relatively mild disease activity of the subjects [35].

4.2. Pathogenesis

Interleukin-1β (IL-1β), Interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) are pro-inflammatory cytokines which are thought to be pathogenic in RA. These cytokines are also associated with sarcopenia and resting energy expenditure in RA patients as shown in Figure 1 [66,75,76]. Those relationships suggest that the inflammatory response of RA promotes sarcopenia. It has been demonstrated from an animal study that muscle wasting in RA is due to the disease itself but not associated with decreased mobility [77]. The exact mechanism of muscle wasting in RA has not yet been elucidated in detail, but muscle wasting may be due to proteolysis by activated catabolic responses and not due to decreased myogenic responses [78]. In adjuvant-induced arthritis (AIA) rats, which is a model of arthritis-induced muscle wasting, increased gene expression of IL-1β accompanied with up-regulation of E3 ubiquitin ligases (atrogin-1 and muscle RING finger-1; MuRF-1), phosphorylated p38 mitogen-activated protein kinase (MAPK)/p38 MAPK, and active nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) have been reported [75]. It is known that NF-κB and p38 MAPK activate the ubiquitin proteasome system [79]. These signaling pathways are related to muscle wasting in RA and they might be activated by IL-1β [75]. In contrast, myogenic regulatory factors such as MyoD, paired box 7 (Pax7), and myogenin are also increased in animals with muscle wasting [75]. These results suggest that muscle repair or anabolic compensation occur simultaneously with muscle wasting.

**Figure 1. Mechanisms of sarcopenia and metabolic modifications in rheumatoid arthritis**

**Figure 1.** Mechanisms of sarcopenia and metabolic modifications in rheumatoid arthritis

IGF-1, insulin-like growth factor-1; IGFBP, insulin-like growth factor-binding protein; IL-1, interleukin-1; TNF-α, tumor necrosis factor-α; GC, glucocorticoid; GR, glucocorticoid receptor; gp 130, glycoprotein 130; Pax7, paired box 7; PI3K, phosphoinositide 3-kinase; mTOR, mammalian target of rapamycin; MAPK, mitogen-activated protein kinase; IKK, IκB kinase; IκB, inhibitor of nuclear factor kappa B; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; JAK, Janus kinase; STAT3, signal transducer and activator of transcription 3; MuRF-1, muscle RING finger 1; UPS, ubiquitin proteasome system.

4.3. Treatments

Although available drugs for sarcopenia do not exist, it seems that treatment for RA is also helpful for RA associated sarcopenia (Table 2). Although there are conflicting results indicating that the use of disease-modifying antirheumatic drugs (DMARDs) is not related to changes in body composition [28], a recent study has revealed that the use of biologic DMARD is negatively associated with sarcopenia in RA [37]. A therapeutic possibility of a biologic DMARD, tocilizumab (anti-IL6 receptor antibody), was also proposed in other studies. From a prospective study in RA patients, a year of treatment with tocilizumab increased lean mass and SMI [30] In addition, AIA rat studies suggested the possibility that β2-adrenoceptor agonist (formoterol) [80], antioxidants [81] and neuromuscular electrical stimulation [82] could prevent skeletal muscle dysfunction or muscle loss in RA. In contrast, the treatment of RA using glucocorticoids (GCs) seems to exacerbate sarcopenia. It has been reported that GCs use was positively associated with low lean mass or sarcopenia in RA patients [32,72]. In a chronic polyarthritis mouse model, GCs treatment prevented inflammatory bone loss but significantly increased muscle wasting [83]. A recent study by Yamada et al. revealed that after administration of GCs for a year, 13.4% of the patients developed sarcopenia [84]. Also, an average GCs use at ≥3.25 mg/day over a year was significantly associated with sarcopenia with a OR of 8.81 (95% CI 1.14-67.9, p=0.037) [84]. Those results imply that GCs treatment in RA patients should be cautious and that reduction or stopping of GCs administration may alleviate treatment related sarcopenia. However, the duration of steroid use was not associated with sarcopenia [34].

**Table 2.** Study findings related to sarcopenia in patients with rheumatoid arthritis.

|  |
| --- |
| Associated factors |
| Age [36,37]  BMI [34–36]  Body fat mass [32,35]  Disease duration [37,74]  Bone erosion/ mineral density [34,36]  Malnutrition/protein intake [37,72]  Joint damage [28,31,37]  Functional status (HAQ score) [26,28,31,72,73]  CRP level [28,36,68,72]  ESR [68,72]  RF [26,28]  MMP3 [35]  Use of GC [32,72,83,84] |
| Treatment |
| IL-6 inhibitor (TCZ) [30]  DMARDs [28,37]  β2-adrenoceptor agonist (Formoterol) [80]  Antioxidant [81]  Neuromuscular electrical stimulation [82] |
| Risk |
| Falls [37]  Fractures [37]  Low bone mineral density [37]  Cardiometabolic risk [34]  Endothelial dysfunction [70] |
| Cytokines/ Pathways |
| IL-1β [66,75]  IL-6 [76]  TNF- α [66,76]  NF-Κb [75]  p38 MAPK [75]  pSTAT3 [75]  Pax7 [75]  Myostatin [75]  MyoD [75,78]  Myogenin [75,78]  IGFBP-5 [78]  IGFBP-3 [78]  atrogin-1 [75,78]  MuRF-1 [75,78] |

BMI, body mass index; HAQ, health assessment questionnaire; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; RF, rheumatoid factor; MMP3, matrix metallopeptidase 3; GC, glucocorticoid; IL-6, interleukin-6; TCZ, tocilizumab; DMARDs, disease-modifying antirheumatic drugs; IL-1β, interleukin-1β; TNF-α, tumor necrosis factor-α; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; MAPK, mitogen-activated protein kinase; pSTAT3, phospho-signal transducer and activator of transcription 3; Pax7, paired box 7; IGFBP, insulin-like growth factor-binding protein; MuRF-1, muscle RING finger 1.

5. Other rheumatic diseases and sarcopenia

5.1. Spondyloarthritis

SpA is a group of rheumatic diseases characterized by inflammation in the axial skeleton and peripheral joints, and by specific clinical symptoms such as uveitis and psoriasis [85]. SpA includes AS, PsA, and other diseases, but previous studies only investigated sarcopenia in AS and PsA. As in other rheumatic diseases, patients with SpA are susceptible to sarcopenia [86], and it was associated with two major factors (Table 3). First, sarcopenia is associated with disease activity which is assessed by Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). Aguiar et al. highlighted that SMI and BASDAI have a significant negative correlation in male AS and PsA patients [86]. In addition, Bath Ankylosing Spondylitis Functional Index (BASFI) was also correlated with sarcopenia in males [86]. Another study confirmed that in AS patients, sarcopenia was associated with BASDAI [38]. Second, sarcopenia is associated with bone mineral abnormality. Sarcopenic PsA patients had a significantly higher prevalence of osteoporosis than non-sarcopenic PsA patients [24]. Another study showed that sarcopenia was associated with lower bone mineral density in AS patients supporting this assumption [38]. On the other hand, other factors such as disease duration was not associated with sarcopenia.

5.2. Systemic sclerosis

SSc is an autoimmune rheumatic disease characterized by vasculopathy, tissue fibrosis and internal organ involvement [87]. SSc patients tend to have decreased muscle strength and endurance related to physical functional disability [88] and 20.7-54.8% of patients exhibit sarcopenia [39–41]. Sarcopenia in SSc was associated with multiple organ involvements of the disease including lung, skin, esophagus, microvasculature, and urinary tracts (Table 3) [39,41,87]. Among the specific characteristics of SSc, longer duration of disease was also associated with sarcopenia [39,41,89]. Besides, low physical function [40], malnutrition [41], and high ESR [41] were also associated with sarcopenia similarly to the findings in RA (Table 3). In particular, elevated ESR in SSc reflects disease severity well [90]. Considering all these results, sarcopenia seems to be related to the progression and severity of SSc. Also, muscle weakness and atrophy could result directly from muscle involvement of SSc [91]. Thus, there might be a considerable overlap in domains of sarcopenia and muscle involvement in SSc. What’s interesting is that sarcopenic patients receive more immunosuppressive drugs than non-sarcopenic patients [40]. It is counterintuitive that alleviating disease activity with immunosuppressive drugs are more related to sarcopenia. Siegert et al. interpreted that receiving more drugs indicates a more severe state and a longer duration of disease [40]. Also, another study indicated that polypharmacy itself might directly contribute to the sarcopenia [92]. However, the association between the use of multiple immunosuppressive drugs and sarcopenia needs further studies. Interventional studies are still scarce but there is a single study highlighting that medical nutrition therapy reversed sarcopenia in patients with GI tract involvement of SSc [93].

**Table 3.** Associated factors related to sarcopenia in patients with rheumatic diseases other than rheumatoid arthritis.

|  |
| --- |
| Spondyloarthritis |
| BASDAI (in AS and male SpA) [38,86]  BASFI (in male SpA) [86]  Bone mineral density (in AS) [38]  Osteoporosis (in PsA) [24] |
| Systemic sclerosis |
| Lung involvement (Medsger severity score) [39]  Skin involvement (mRSS, Medsger severity score) [39,41]  Microvascular involvement (capillaroscopy score) [41]  Esophageal involvement [41]  Overactive bladder [87]  Disease duration [39,41,89]  DLCO [39,41]  Malnutrition [41]  ESR [41] |

BASDAI, Bath Ankylosing Spondylitis Disease Activity; BASFI, Bath Ankylosing Spondylitis Function Index; mRSS, modified Rodnan Skin Score; DLCO, diffusing capacity for carbon monoxide; ESR, erythrocyte sedimentation rate.

6. Inflammatory bowel disease and sarcopenia

IBD includes CD and UC which are characterized by chronic relapsing bowel inflammation. The etiology of IBD remains unclear but environmental and genetic factors seem to be involved in autoimmune pathogenicity [94,95]. In IBD patients, sarcopenia is frequent and the muscle mass reduces over time accompanied by an increased BMI [96,97]. According to a follow up study, the prevalence of sarcopenia has increased from 9.3 to 16.3% until a year after the diagnosis although sarcopenia did not increase after that time [97]. Sarcopenia in IBD has been studied for its prognostic implication. It has been considered as a predictive factor for medical rescue therapy and bowel resection [43,45,46], and postoperative complications [47,52,98,99] in both CD and UC. Also in CD, sarcopenia is associated with primary non-response to anti-TNF treatment, and therefore sarcopenic IBD patients need adjusted dosing [100]. The mechanism of sarcopenia in IBD patients is believed to be associated with disease related inflammation and nutritional problems. Muscle radiation attenuation, which is an inverse parameter of muscle fat content [101], is associated with severe phenotypes of disease such as history of a stricturing, penetrating complication, or previous resection surgery in CD [51]. In addition, sarcopenia is associated with high disease activity assessed by Mayo score in UC [42]. Inflammatory markers such as CRP and ESR, were associated with sarcopenia in IBD [50,99]. Also, vitamin D in pediatric patients, hemoglobin and albumin in adult patients were associated with sarcopenia [44,50]. Decreased motility also seems to contribute to sarcopenia in pediatric patients [102]. In addition, we suggest a possibility that the gut microbiome might be related to sarcopenia in IBD. In IBD, the composition and function of microbiome are altered. It has been reported that IBD patients have increased pro-inflammatory bacterial species (Escherichia, Fusobacterium) and decreased anti-inflammatory bacterial species (Faecalibacterium) with decreased amino acid biosynthesis of the microbiome [103]. In addition, it has been suggested that the gut microbiome could directly affect the muscle by modulating amino acid bioavailability and the production of pro-inflammatory cytokines [104]. In an acute leukemia mouse model, oral supplementation of lactobacillus species decreased atrogin-1, MuRF1 and inflammatory cytokines [105]. A direct association of muscle and gut microbiome in sarcopenic IBD should be investigated by animal and clinical studies. To alleviate sarcopenia in IBD, treatment of the disease through reduction in inflammation would be effective. Infliximab, a TNF-α antibody, increased both muscle volume and strength in CD patients [106], and moreover, colectomy increased SMI and serum albumin with decrease in the prevalence of sarcopenia in UC patients [42]. Nutritional management might be also needed for better postoperative prognosis in sarcopenic IBD patients, although it is not effective directly in the management of sarcopenia [47].

7. Autoimmune diabetes and sarcopenia

T1DM is a chronic autoimmune disease characterized by hyperglycemia due to pancreatic islet β-cell destruction [107]. T1DM patients have a high prevalence of sarcopenia and hyperglycemia is linked with low muscle function [53,108]. There are many factors that contribute to muscle dysfunction in diabetes. Excessive intramyocellular lipid (IMCL) lowers muscle quality and might impair muscle function [109]. Increased IMCL is frequently observed in T1DM patients [110]. Especially, increased IMCL is associated with poor glycemic control evaluated by Hemoglobin A1c (HbA1c) [111]. Accumulation of advanced glycation end-products, which are associated with persistent hyperglycemia [112], is also thought to contribute to low muscle function in T1DM patients [53]. In addition, it has been reported that hyperglycemia is linked with muscle atrophy via a WW domain containing E3 ubiquitin protein ligase 1 (WWP1)/ Krüppel-like factor 15 (KLF15) pathway [113]. Hyperglycemia inhibits degradation of KLF15 via downregulation of WWP1 and increased KLF15 promotes proteolysis via upregulation of atrogin-1 and MuRF1 [113,114]. Moreover, hormones or cytokines that are related to skeletal muscle are altered in T1DM. Diabetic patients appear to have higher GC and IL-6 levels and both have catabolic effects [115–117]. Moreover, Insulin-like growth factor-1 (IGF-1) which is well known for its contribution to skeletal muscle regeneration and development is decreased with alteration of IGFBP [118–120]. Recently, mitochondrial dysfunction in T1DM has been suggested as a primary contributor to muscle dysfunction. Mitochondrial changes in T1DM related sarcopenia is similar to that in age-related ones, and both includes elevated oxidative stress and mitochondrial-induced cell death [121]. LADA is a subtype of T1DM but has insulin resistance similar to type 2 diabetes mellitus (T2DM) [122]. LADA had a higher risk of sarcopenia compared to controls and even T2DM groups in a cross-sectional study, but the association between LADA and sarcopenia has not been elucidated in great detail so far [54].

5. Conclusions

In this in-depth review, we provide evidence that sarcopenia is common in different autoimmune and rheumatic diseases. The exact prevalence differs between different studies, in part due to different definitions of sarcopenia used. We propose that reporting sarcopenia in autoimmune and rheumatic disorders is essential, since it contributes to morbidity and mortality among these patients. Specific risk factors need to be confirmed in larger studies with a particular focus on treatment strategies, i.e. cumulative dose of GC or other immunosuppressive measures. More detailed analyses highlighting the role of chronic inflammation in the propagation of sarcopenia are needed.

**Supplementary Materials:** Supplementary materials can be found at [www.mdpi.com/xxx/s1](http://www.mdpi.com/xxx/s1).

Table S1. Study findings of rheumatoid arthritis and sarcopenia

Table S2. Study findings of rheumatic diseases other than rheumatoid arthritis and sarcopenia

Table S3. Study findings of inflammatory bowel disease and sarcopenia

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Abbreviations

|  |  |  |
| --- | --- | --- |
| ICD |  | International Classification of Diseases |
| OR |  | Odds ratio |
| RA |  | Rheumatoid arthritis |
| SMI |  | Skeletal muscle mass index |
| ASM |  | Appendicular skeletal muscle mass |
| EWGSOP |  | The European Working Group on Sarcopenia in Older People |
| FNIH |  | The Foundation of the National Institute of Health |
| IWGS |  | The International Working Group on Sarcopenia |
| ESPEN SIG |  | The European Society on Clinician Nutrition and Metabolism special interest groups |
| AWGS |  | The Asian Working Group for Sarcopenia |
| EWGSOP2 |  | The European Working Group on Sarcopenia in Older People 2 |
| FFMI |  | Free fat mass index |
| PsA |  | Psoriatic arthritis |
| TUG |  | Timed up and go |
| SpA |  | Spondyloarthritis |
| AS |  | Ankylosing spondylitis |
| SLE |  | Systemic lupus erythematosus |
| SSc |  | Systemic sclerosis |
| IBD |  | Inflammatory bowel disease |
| CT |  | Computed tomography |
| UC |  | Ulcerative colitis |
| CD |  | Crohn’s disease |
| T1DM |  | Type 1 diabetes mellitus |
| LADA |  | Latent autoimmune diabetes in adults |
| HAQ-DI |  | Health Assessment Questionnaire Disability Index |
| CRP |  | C-reactive protein |
| ESR |  | Erythrocyte sedimentation rate |
| IL-1β |  | Interleukin-1β |
| IL-6 |  | Interleukin-6 |
| TNF-α |  | Tumor necrosis factor-α |
| AIA |  | Adjuvant-induced arthritis |
| MuRF-1 |  | Muscle RING finger-1 |
| MAPK |  | Mitogen-activated protein kinase |
| NF-κB |  | Nuclear factor kappa-light-chain-enhancer of activated B cells |
| Pax-7 |  | Paired box 7 |
| DMARD |  | Disease-modifying antirheumatic drug |
| GC |  | Glucocorticoid |
| BASDAI |  | Bath Ankylosing Spondylitis Disease Activity Index |
| BASFI |  | Bath Ankylosing Spondylitis Functional Index |
| IMCL |  | Intramyocellular lipid |
| WWP1 |  | WW domain containing E3 ubiquitin protein ligase 1 |
| KLF15 |  | Krüppel-like factor 15 |
| IGF-1 |  | Insulin-like growth factor-1 |
| IGFBP |  | Insulin-like growth factor-binding protein |
| T2DM |  | Type 2 diabetes mellitus |

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**Sarcopenia in autoimmune and rheumatic diseases: a comprehensive review**

**Table S1**. Study findings of rheumatoid arthritis and sarcopenia

**Table S2**. Study findings of rheumatic diseases other than rheumatoid arthritis and sarcopenia

**Table S3**. Study findings of inflammatory bowel disease and sarcopenia

**Table S1.** Study findings of rheumatoid arthritis and sarcopenia

|  |  |  |
| --- | --- | --- |
| Author | Study findings | Definition of Sarcopenia |
| Vulnerability | | |
| Dao et al. [1] | Female early RA patients in Vietnam had lower appendicular LM. | FFMI (Hull et al. [2]) |
| Doğan et al. [3] | Female RA patients had lower SMI and higher sarcopenia prevalence. | SMI (Janssen et al. [4]) |
| Santo et al. [5] | According to meta-analysis, rheumatoid cachexia is a common comorbidity in RA whose prevalence is 15-32%. | - |
| Munro et al. [6] | RA patients had lower upper arm muscle mass. | - |
| Kasher et al. [7] | Female RA patients in Kazakhstan had lower MMI. | - |
| Associated factors | | |
| Dao et al. [1] | Disease activity, functional status, RF seropositivity was associated with abnormal body composition in female RA patients. | FFMI (Hull et al. [2]) |
| Giles et al. [8] | CRP levels, RF seropositivity, joint deformity, functional limitation was associated with abnormal body composition in RA patients. | SMI (Janssen et al. [4]) |
| Ngeuleu et al. [9] | Bone erosion, normal/over fat BMI were associated to sarcopenia but disease activity and functional status were not associated in RA patients. | SMI (Baumgartner et al. [10]) |
| Lin et al. [11] | Functional limitation (HAQ‐DI > 1) and joint damage were positively associated with sarcopenia in RA patients. | SMI (AWGS [12]) |
| Tada et al. [13] | BMI, body fat mass, and MMP3 were associated with sarcopenia in RA patients. | AWGS [12] |
| Mochizuki et al. [14] | Age, BMI, CRP, hip bone mineral density were significantly associated with sarcopenia in RA patients. | AWGS [12] |
| Torii et al. [15] | Age, longer disease duration, joint destruction and malnutrition were associated with sarcopenia in RA patients. | EWGSOP [16], AWGS [12] |
| Vlietstra et al. [17] | Higher body fat was associated with sarcopenia but self-reported fatigue and physical function were not associated in RA patients. | SMI (FNIH [18]) |
| Munro et al. [6] | The acute phase response (ESR, CRP) had a significant correlation with reduced fat free mass in female RA patients. | - |
| Müller et al. [19] | Higher ESR, CRP, lower protein intake, worse functional status were associated with having low lean mass in early RA patients. | ALM/height2  (male< 8.0586 kg/h2 female< 6.0359 kg/h2 ) |
| Alkan Melikoğlu [20] | SMI of RA patients had a negative correlation with functional status. | - |
| Beenakker et al. [21] | The low handgrip strength was negatively associated with disease duration but not associated with age between 35 and 65 years in RA patients. | - |
| Drugs/Treatment | | |
| Giles et al. [8] | Not using DMARDs was associated with abnormal body composition in RA patients. | SMI (Janssen et al. [4]) |
| Ngeuleu et al. [9] | There was no significant difference according to duration of steroid use between sarcopenic and non-sarcopenic RA group. | SMI (Baumgartner et al. [10]) |
| Tournadre et al. [22] | TCZ was effective in gain of weight, lean mass, appendicular lean mass and SMI without fat mass gain in RA patients. | SMI (Baumgartner et al. [10]) |
| Torii et al. [15] | Use of bDMARDs was negatively associated with sarcopenia in RA patients. | EWGSOP [16], AWGS [12] |
| Vlietstra et al. [17] | GC use was associated with sarcopenia in RA patients. | SMI (FNIH [18]) |
| Müller et al. [19] | Current GC use was associated with having low lean mass in the early RA group. | ALM/height2  (male< 8.0586 kg/h2 female< 6.0359 kg/h2 ) |
| Gómez-SanMiguel et al. [23] | In AiA rats, formoterol administration decreased severity of disease and skeletal muscle loss. It was associated with decreased inflammation, myostatin, the p-NF-κB(p65)/TNF pathway, IGFBP-3 and increased Akt and myogenin. | - |
| Yamada et al. [24] | According to an animal study of AiA rats, antioxidant treatment could prevent skeletal muscle dysfunction in RA patients. | - |
| Himori et al. [25] | According to an animal study of AiA rats, neuromuscular electrical stimulation could prevent skeletal muscle dysfunction in RA patients. | - |
| Fenton et al. [26] | In mice models of chronic polyarthritis, GC increased muscle wasting but reduced bone loss. | - |
| Yamada et al. [27] | GC use could promote sarcopenia in RA patients. | AWGS [12] |
| Risk | | |
| Ngeuleu et al. [9] | Sarcopenia was associated with cardiometabolic risk in RA patients | SMI (Baumgartner et al. [10]) |
| Torii et al. [15] | The incidence of falls, fractures, and lower bone mineral density were higher in patients with sarcopenia. | EWGSOP [16], AWGS [12] |
| Delgado-Frías et al. [28] | Sarcopenia in RA patients was associated with lower endothelial function. | SMI (Janssen et al. [4]) |
| Mechanism | | |
| Roubenoff et al. [29] | Loss of body cell mass, high TNF-α and IL-1 were observed and cytokine production was associated with resting energy expenditure in RA patients. | - |
| Little et al. [30] | In AiA rabbits, reduction of muscle mass and diameter seem to be related with increased IL-1β, NF-κB, p38 MAPK signaling and seem to trigger anabolic compensation of increased myonuclei, Pax7, MyoD, myogenin and reduced pSTAT3, myostatin. | - |
| Visser et al. [31] | Higher plasma concentrations of IL-6 and TNF-α were associated with lower muscle mass and muscle strength. | - |
| de Oliveira Nunes Teixeira et al. [32] | In a CIA rat study, muscle atrophy was not associated with decreased mobility. | - |
| Castillero et al. [33] | In AiA rats, arthritis-induced skeletal muscle atrophy may be due to proteolysis resulting from increased IGFBP-5, IGFBP-3, atrogin-1 and MuRF-1 but not from a decrease in the myogenic regulatory factors. | - |

LM, lean mass; FFMI, free fat mass index; SMI, skeletal muscle mass index; MMI, muscle mass index; RF, rheuatoid factor; CRP, C-reactive protein; BMI, body mass index; HAQ-DI, health assessment questionnaire disability index; MMP3, matrix metallopeptidase 3; ESR, erythrocyte sedimentation rate; ALM, appendicular lean mass; DMARD, disease-modifying antirheumatic drug; TCZ, tocilizumab; bDMARD, biologic disease-modifying antirheumatic drug; GC, glucocorticoid; AiA, adjuvant-induced arthritis; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; TNF, tumor necrosis factor; IGFBP, insulin-like growth factor-binding protein; IL-1, interleukin-1; MAPK, mitogen-activated protein kinase; Pax7, paired box 7; pSTAT3, phospho-signal transducer and activator of transcription 3; IL-6, interleukin-6; CIA, collagen-induced arthritis; MuRF-1, muscle RING finger 1.

**Table S2.** Study findings of rheumatic diseases other than rheumatoid arthritis and sarcopenia

|  |  |  |
| --- | --- | --- |
| Author | Findings | Definition of sarcopenia |
| Spondyloarthritis | | |
| El Maghraoui et al. [34] | Sarcopenia and pre-sarcopenia associated with high BASDAI and low BMD in AS patients. | EWGSOP [16] |
| Krajewska-Włodarczyk et al. [35] | Sarcopenia was associated with occurrence of osteoporosis in PsA patients. | SMI (Janssen et al. [36]), TUG>14s |
| Aguiar et al. [37] | SMI was correlated with BASDAI and BASFI in male patients. | SMI (Male: <10.75, Female: 6.75) |
| Systemic sclerosis | | |
| Caimmi et al. [38] | Sarcopenia was associated with longer disease duration, worse DLCO/VA, lung and skin involvement (Medsger severity score). | SMI (Baumgartner et al. [10]) |
| Siegert et al. [39] | Sarcopenic patients had lower physical function and more immunosuppressive drugs than non-sarcopenic patients. | EWGSOP [16] |
| Corallo et al. [40] | When defining sarcopenia according to SMI and HS separately, both were associated with malnutrition, disease duration, mRSS, capillaroscopy score, esophageal involvement, ESR and DLCO. | SMI (Baumgartner et al. [10]) or HS (Male: <30, Female:<20) |
| Pacini et al. [41] | Sarcopenia is positively correlated with overactive bladder. | SMI (Baumgartner et al. [10]) |
| Justo et al. [42] | Female SSc patients had reduced muscle strength, endurance and it was correlated with physical disability. | - |
| Marighela et al. [43] | Longer disease duration was correlated with SMI. | SMI (Baumgartner et al. [10]) |
| Doerfler et al. [44] | Medical nutrition therapy intervention reversed sarcopenia in GI involvement patients. | SMI (Baumgartner et al. [10]) |

BASDAI, Bath Ankylosing Spondylitis Disease Activity; BMD, bone mineral density; BASDFI, Bath Ankylosing Spondylitis Function Index; DLCO, diffusing capacity for carbon monoxide; VA, alveolar volume; mRSS, modified Rodnan Skin Score; GI, gastrointestinal.

**Table S3.** Study findings of inflammatory bowel disease and sarcopenia

|  |  |  |
| --- | --- | --- |
| Author | Findings | Definition of sarcopenia |
| Inflammatory bowel disease (no separation into CD and UC) | | |
| Adams et al. [45] | Sarcopenia is a predictor of need for surgery. | SMI (Prado et al. [46]) |
| Bryant et al. [47] | SMI continuously decreased over time in newly diagnosed IBD patients, while sarcopenia did not. | SMI, HS (EWGSOP [16]) |
| Pedersen et al. [48] | Sarcopenia is a predictor of postoperative complications in patients younger than 40 years. | Lowest sex quartile of TPI or HUAC. |
| Werkstetter et al. [49] | Pediatric IBD patients have lower lean body mass, muscle strength and reduced physical activity. | - |
| Crohn’s disease | | |
| Mager et al. [50] | In children with IBD, sarcopenia is more prevalent in CD than UC.  Sarcopenia is associated with suboptimal vitamin D levels (<50 nmol/l) in CD. | SMM z score<-2 [51] |
| Zhang et al. [52] | Sarcopenia is a predictor of major postoperative complications (grade ≥ III on the Clavien-Dindo scale[53]). | SMI (Fearon et al. [54]) |
| Bamba et al. [55] | Sarcopenia is a predictor of need for surgery. | SMI (Nishikawa et al. [56]) |
| Thiberge et al. [57] | SMI was non-significantly lower in the group of patients needing surgery or dying during follow-up. | SMI (Mourtzakis et al. [58]) |
| Lee et al. [59] | CRP was associated with sarcopenia and ESR, serum albumin, hemoglobin were correlated with SMI. | SMI (Kim et al. [60]) |
| Cravo et al. [61] | Lower muscle attenuation was associated with severe phenotypes (stricturing or penetrating) | SMI (Martin et al. [62]) |
| Carvalho et al. [63] | Sarcopenia is a predictor of postoperative complications. | SMI (Prado et al. [46]) |
| Ding et al. [64] | Sarcopenia was associated with primary nonresponse to anti-TNF therapy | Lowest sex quartile of SMI. |
| Subramaniam et al. [65] | Infliximab increased muscle volume and strength. | - |
| Ulcerative colitis | | |
| Zhang et al. [66] | Sarcopenia was associated with high disease activity (high Mayo score) and colectomy reversed sarcopenia. | SMI (Fearon et al. [54]) |
| Cusing et al. [67] | Sarcopenia is a predictor of need for medical rescue therapy or surgery in hospitalized ASUC patients. | SMI (Fearon et al. [54]) |
| Fujikawa et al. [68] | Sarcopenia is a predictor of surgical site infection.  Sarcopenia is associated with CRP. | Lowest sex quartile of TPI. |

TPI, total psoas index; HUAC, Hounsfield unit average calculations; ASUC, acute severe ulcerative colitis.

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