<u>Viewpoint</u>

Systemic Inflammation and Disruption of the Local Microenvironment Compromise Muscle Regeneration: Critical Pathogenesis of Autoimmune-Associated Sarcopenia

Yingjuan Zhang[1*], MSc; Qingqian Wu[1*], PhD; Yi Wang[2*], BSc; Qingyan Chen[3], BSc; Shuang Han[1], PhD; Bei Li[1], PhD; Qingwen Zhao[1], PhD; Qianzhuo Wang[1], BSc; Yule Wang[1], PhD; Yue Gao[1], BSc

[1]Department of Geriatrics, Zhejiang Key Laboratory of Traditional Chinese Medicine for the Prevention and Treatment of Senile Chronic Diseases, Affiliated Hangzhou First People's Hospital, School of Medicine, Westlake University, Hangzhou, China
[2]Yixing Center for Disease Control and Prevention, Yixing, Jiangsu Province, China
[3]Fourth Clinical School of Medicine, Zhejiang Chinese Medical University, Hangzhou, China
*these authors contributed equally

Corresponding Author:

Yue Gao, BSc
Department of Geriatrics
Zhejiang Key Laboratory of Traditional Chinese Medicine for the Prevention and Treatment of Senile Chronic Diseases,
Affiliated Hangzhou First People's Hospital, School of Medicine, Westlake University
261 Huansha Road, Shangcheng District
Hangzhou, 310006
China
Phone: 86 13706511908
Email: gaoyue@hospital.westlake.edu.cn

Abstract

Sarcopenia is defined by age-related reductions in muscle mass, strength, and physiological function, and it is especially prevalent among individuals with autoimmune diseases. Autoimmune disorders, characterized by immune dysregulation, cause systemic inflammation and damage to multiple tissues through unregulated immune activity. Research indicates that autoimmune diseases negatively impact skeletal muscle functions and may worsen the progression of sarcopenia. This viewpoint comprehensively discusses the pathogenesis and potential mechanism of sarcopenia in 3 autoimmune diseases: inflammatory bowel disease, rheumatoid arthritis, and type 1 diabetes mellitus. Mechanistically, chronic immune microenvironment alterations induce compartment-specific redistribution of leukocyte subsets and cytokine networks. These perturbations disrupt critical signaling pathways governing muscle protein synthesis, satellite cell activation, and mitochondrial bioenergetics, leading to impaired regeneration and accelerated sarcopenia progression. By delineating shared and distinct pathomechanisms across these models, this analysis reframes our understanding of immune-mediated muscle wasting. Beyond mechanistic insights, it establishes a translational framework for targeted therapies and highlights emerging research directions bridging immunology and age-related musculoskeletal decline.

Introduction

Sarcopenia is an age-related syndrome characterized by progressive and systemic loss of skeletal muscle mass and strength [1]. The decline of skeletal muscle function caused by sarcopenia has aroused widespread concern [2]. Maintaining skeletal muscle mass and integrity is essential for the proper functioning of the musculoskeletal system and for the effective absorption and storage of nutrients [3]. Sarcopenia has a significant impact on general health, with numerous important effects. It is closely related to the development of exercise-related diseases, such as falls, fractures, and disabilities [4]. Additionally, it is also associated with adverse outcomes such as cardiovascular diseases [5], metabolic diseases, and even death [6]. However, the exact cause of primary sarcopenia is not fully understood yet. Recent studies suggested that cellular aging [7], mitochondrial disorder [8], decreased physical activity [9], and excessive caloric intake

could accelerate the progression of sarcopenia. Moreover, an imbalance of oxygen in the body may contribute to the development of sarcopenia as well [10].

Sarcopenia afflicts not only the older people but also the patients with immune diseases. Studies have shown that immune diseases such as type 1 diabetes mellitus (T1DM), rheumatoid arthritis (RA), inflammatory bowel disease (IBD), spinal arthritis, and systemic sclerosis are often associated with sarcopenia [11]. Autoimmune diseases combined with sarcopenia are closely related to adverse clinical outcomes, poor effects of treatment and prognosis, and low quality of life [12]. Current research efforts have concentrated on the high prevalence of sarcopenia among autoimmune disease patients and its associated adverse prognosis. Studying the relationship between sarcopenia and autoimmune diseases is crucial, as is clarifying the incidence and pathogenesis of sarcopenia linked to immune disorders. Immune disorders regulate key cascades like JAK/STAT (Janus kinase/signal transducers and activators of transcription) by influencing immune cells, profoundly impacting muscle protein synthesis and metabolism. This is a crucial factor in the pathogenesis of autoimmune diseases accompanied by muscular atrophy. Previous studies have focused on the differences in performance between healthy and sick individuals through case-control analysis. However, our comprehensive and in-depth analysis shows that focusing on immune cells and the related factors released and exploring the pathogenesis of diseases based on this, to find effective targeted therapies, will become a new and promising direction for the study of autoimmune diseases and sarcopenia. The elucidation of these underlying mechanisms may pave the way for novel research avenues in understanding the pathophysiology of sarcopenia associated with autoimmune disorders, while simultaneously offering crucial mechanistic insights to inform the development of targeted therapeutic interventions with enhanced precision. This study aims to provide a theoretical foundation and new avenues for future research.

Sarcopenia

In 1989, Irwin Rosenberg first described sarcopenia as the loss of muscle mass that occurs with aging [13]. With the deepening of research, sarcopenia is generally recognized as a progressive and systemic skeletal muscle disease manifested by accelerated loss of muscle mass and function [14]. The European Working Group on Sarcopenia in Older People 2 updated the definition of sarcopenia to account for muscle mass, muscle strength, and motor function performance for the first time [13]. The European Working Group on Sarcopenia in Older People 2 suggests that sarcopenia may be present when muscle strength is insufficient, and can be diagnosed when low muscle quantity or quality exist simultaneously [13]. Moreover, when the patient has low muscle mass, low muscle strength, and weak motor function at the same time, severe sarcopenia can be diagnosed [15]. Applying Western diagnosis criteria to Asian people may not be adequate. For special considerations such as different body sizes, fat distribution, and physical activity from the Asians,

the Asia Working Group for Sarcopenia proposed and revised an algorithm for diagnosing sarcopenia based on the Asian data [1,16] (Figure 1).

The prevalence of sarcopenia in older individuals within community health care settings has been reported to reach up to 29% [16]. Aging changes the homeostasis of skeletal muscle and disturbs the balance between anabolic and catabolic processes on the protein production pathway [16]. Sarcopenia is characterized by a decrease in the size and number of satellite cells and the atrophy of type 2 muscle fibers. Sarcopenia is distinct from malnutrition and cachexia, although each exhibits interrelated pathophysiology leading to different magnitudes of "wasting" and susceptibility to cardiovascular events (Table 1) [2].

Diagnosing sarcopenia requires a combined measurement of muscle mass, strength, and physical performance [17] (Figure 1). At present, imaging methods, such as computed tomography, dual-energy x-ray absorptiometry (DXA), and magnetic resonance imaging are used for muscle mass detection [18]. However, those instruments are expensive, time-consuming, and laborious. Besides, computed tomography detection has a certain level of radioactivity, which limits its application in clinical practice and population research [19]. DXA can distinguish adipose tissue from other soft tissues and measure the volume of tissues and organs accurately, so it is suitable for different populations and is considered the "gold standard" for measuring muscle mass [20]. Owing to the characteristics of fast, convenient, and low radioactivity, DXA is also frequently used for body composition detection. However, DXA has the limitations of not assessing muscle quality (ie, muscle fat infiltration), and DXA measurements may be influenced by the patient's hydration status [21]. The machine requires a large space and is inconvenient to move away, making DXA not an ideal measurement for large-scale clinical trials of sarcopenia, bedside assessments, or community health screening work [18]. Bioelectrical impedance analysis (BIA) is another measurement for muscle mass detection. The principle underlying BIA is that different body compositions at the tissue-organ level exhibit varying electrical conductivity, with skeletal muscle demonstrating good conductivity and adipose tissue showing poor conductivity. This enables BIA to estimate the quantity of body fat and skeletal muscle mass [22]. Comparatively speaking, except inexpensive, BIA is a portable device that can easily perform bedside diagnostics as well. Therefore, BIA is frequently used in many types of studies. As BIA equations and cut-off values are population and device-specific, results can vary between devices and different populations [23]. Moreover, studies showed that the mass of hospitalized older patients was overestimated [24]. Nevertheless, the results of BIA would also be affected by the placement of electrodes, so it is necessary to combine grip strength and walking speed detection to evaluate the occurrence of sarcopenia [25].

Sarcopenia increases the risk of falls, fractures, and death. When combined with other diseases, it can hinder recovery after hospitalization, prolong prognosis recovery time, and increase the economic burden on patients [26]. Previous

studies suggested that sarcopenia and osteoporosis interacted with each other. Compared with healthy people, individuals with sarcopenia have a heightened susceptibility to developing osteoporosis. Conversely, individuals experiencing severe osteoporosis often undergo substantial loss of skeletal muscle mass, thereby increasing their vulnerability to falls and fractures [27]. Sarcopenia is known to adversely affect the outcomes of patients with various forms of cancer. Apart from what is mentioned above, there exists an interaction between sarcopenia and immune diseases. The complication of sarcopenia greatly increases the incidence; mortality; and prognosis of diabetes, arthritis, and IBD.

Figure 1. Simple algorithms for Europeans and Asians to diagnose sarcopenia in clinical practice respectively. ASM: appendicular skeletal muscle mass; BIA: bioelectrical impedance analysis; CT: computed tomography; DXA: dual-energy x-ray absorptiometry; F: female; LMS: low muscle strength; LPP: low physical performance; M: male; MRI: magnetic resonance imaging; SARC-Calf: SARC-F plus calf circumference (score of ≥11 is termed as sarcopenia); SARC-F: strength, assistance in walking, rising from a chair, climbing stairs, and falls (score of ≥4 is termed as sarcopenia).
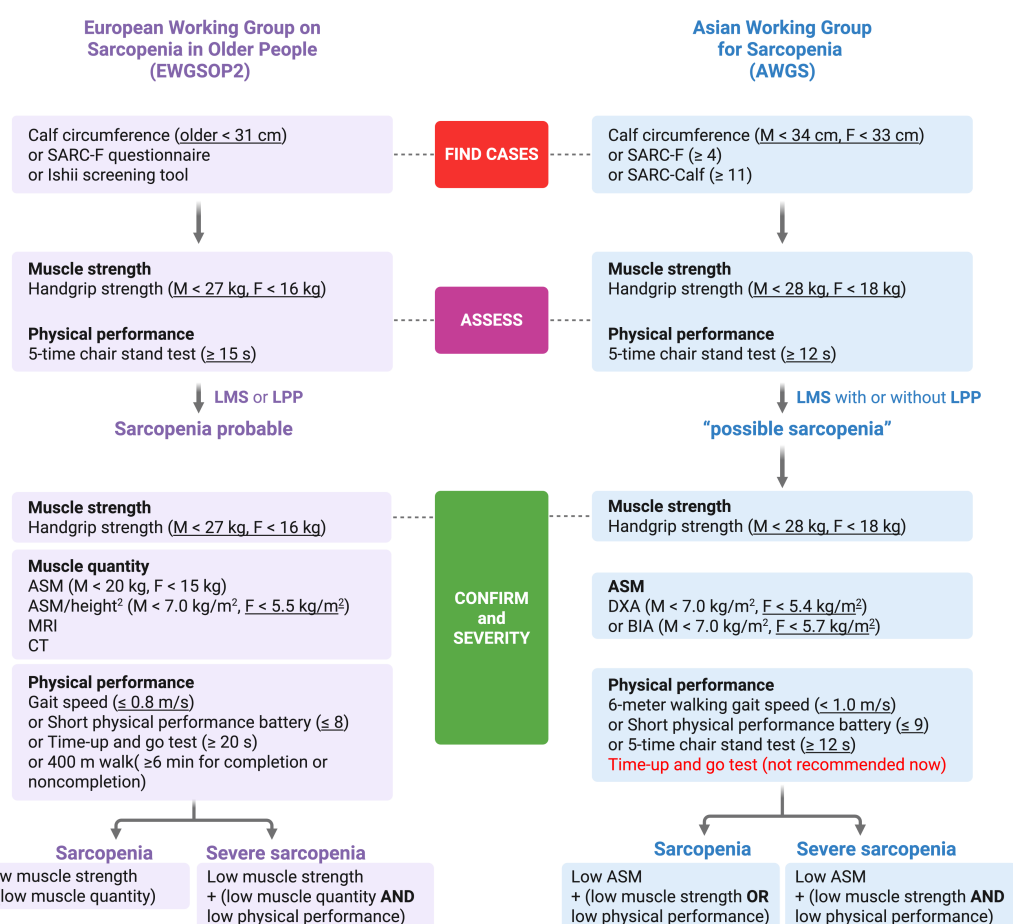
Table 1. Differences between sarcopenia, cachexia, and malnutrition.

	Sarcopenia	Cachexia	Malnutrition
Clinical features	Loss of muscle strength and muscle mass	Weight loss with loss of muscle mass	Weight loss
Functional impairment	Indicate severity	+++[a]	_[b]
Mechanism	Age-related, pathologic	Pathologic	Inadequate caloric intake, malabsorption
Inflammation	+/–[c]	+++	–
Anorexia	+/–	++[d]	+/–
Fat mass	+/–	Decreased	Decreased
Protein degradation	+/–	+++	+[e]

[a]+++: high, a higher degree or intensity of a feature or symptom in the disease.
[b]–: absence of the characteristic/symptom indicates the absence or absence of a characteristic, symptom, or mechanism.
[c]+/–: variable presence or inconsistency across conditions.
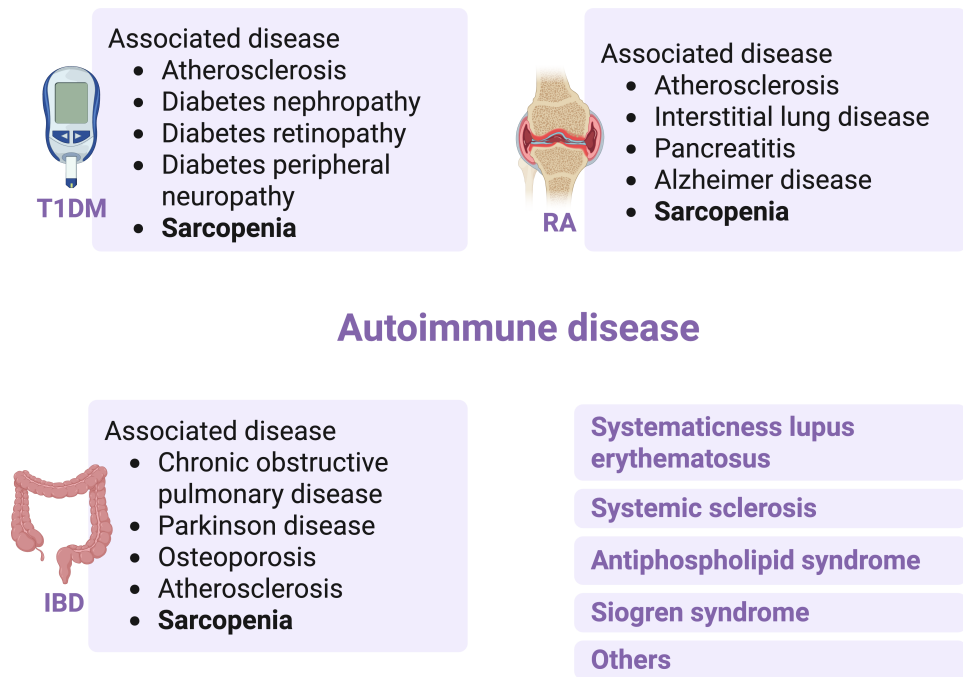[d]++: moderate, the presence or intensity of a characteristic or symptom in the disease.
[e]+: low, a feature or symptom that is less present or intense in the disease.

Autoimmune Diseases

Autoimmune diseases are a series of related diseases characterized by dysregulation of the immune system, in which immune cells cannot distinguish self-antigens from non–self-antigens and give rise to activation of immune cells to attack autoantigens, leading to inflammation and multi-tissue damage [28]. T1DM, RA, and IBD are autoimmune diseases [29]. Moreover, some of the autoimmune diseases are organ-specific, such as primary biliary cirrhosis, and some reflect a variety of immunological dysfunctions involving multiple organ immune dysfunction such as systemic lupus erythematosus [30]. T1DM is dramatically increasing in many parts of the world [31], they affect millions of people and are prone to serious complications such as heart and kidney disease, stroke, and blindness [32] (Figure 2). RA is an autoimmune disease that damages joints and other tissues and organs such as the heart, kidneys, lungs, digestive system, eyes, skin, and nervous system [33]. IBD is a chronic, progressive immune-mediated inflammatory condition of the gastrointestinal tract [34]. The incidence of IBD has rapidly increased worldwide. Patients with IBD may suffer from malnutrition, characterized by an energy or nutrient imbalance, leading to sarcopenia, micronutrient deficiencies, overweight, obesity, and sarcopenic obesity [35]. Sarcopenia is a common complication of autoimmune diseases, and the primary cause is the loss and damage of skeletal muscle induced by immune dysfunction [36-38].

Figure 2. The associated disease of autoimmune diseases. IBD: inflammatory bowel disease; RA: rheumatoid arthritis; T1DM: type 1 diabetes mellitus.

Associated disease
- Atherosclerosis
- Diabetes nephropathy
- Diabetes retinopathy
- Diabetes peripheral neuropathy
- **Sarcopenia**

T1DM

Associated disease
- Atherosclerosis
- Interstitial lung disease
- Pancreatitis
- Alzheimer disease
- **Sarcopenia**

RA

Autoimmune disease

Associated disease
- Chronic obstructive pulmonary disease
- Parkinson disease
- Osteoporosis
- Atherosclerosis
- **Sarcopenia**

IBD

Systematicness lupus erythematosus

Systemic sclerosis

Antiphospholipid syndrome

Siogren syndrome

Others

Type 1 Diabetes Mellitus and Sarcopenia

T1DM results from the autoimmune dysfunction and death of β-cells, requiring lifelong insulin therapy [39]. This condition arises from a complex interaction between invading or resident macrophages and T cells. These immune cells release various substances, such as chemokines and cytokines, in the islet microenvironment that promote the apoptosis of beta cells. Simultaneously, β-cells can attract and activate immune cells to the islet area through their signaling, especially in response to stress, damage, or cell death [40]. The primary consequence of T1DM is hyperglycemia. Research indicates that the insulin-like growth factor (IGF) and IGF-binding protein (IGFBP) axis are crucial in maintaining normal glucose levels. Patients with T1DM showed a significant reduction in serum IGF-I levels. Additionally, mitophagy plays a crucial role in regulating the autoimmune response during the development of T1DM by preventing the accumulation of defective or dysfunctional mitochondria in pancreatic cells [41]. Muscle fibers can be damaged and undergo adverse remodeling due to the hyperglycemic and inflammatory microenvironment caused by T1DM, ultimately leading to sarcopenia [42]. A cross-sectional study showed that the prevalence of sarcopenia in participants aged 65 years or older with T1DM is 42.9%, which is significantly higher than that in people of the same age without sarcopenia [43]. Moreover, musculoskeletal system health would be affected if T1DM was poorly controlled in childhood and adolescence, and then sarcopenia would become the late complication of T1DM in adults [42].

Skeletal muscle is a primary driver organ that maintains whole-body glycemic balance [44]. Poor blood glucose control is the main risk factor for T1DM, which is complicated by sarcopenia [45]. IGFs, especially IGF1 and IGF2, can promote glucose metabolism, with their availability regulated by IGFBPs. In sum, IGFs are dysregulated both before and after the clinical diagnosis of T1DM and may serve

as novel biomarkers to improve disease prediction [46]. Subsequently, Hata et al [47] discovered that a low serum IGF-1 level is associated with sarcopenia and low skeletal muscle mass in subjects with T1DM. Moreover, growth hormone could regulate cell survival and the musculoskeletal system function through growth hormone/IGF1 signaling pathway [48]. Other researchers found that IGF1 activates the AKT/PKB pathway and protein synthesis pathway by binding to the IGF1 receptor, thereby increasing muscle synthesis [49]. In addition, previous reports have pointed out that mitochondrial dysfunction is the common cause of regulating muscle degeneration induced by aging and T1DM [50]. However, increased oxidative stress, decreased respiration and oxidative capacity, and increased permeability pore opening in mitochondria could promote the process of apoptosis.

Rheumatoid Arthritis and Sarcopenia

RA is an autoimmune disease characterized by the presence of symmetrical polyarthritis, which tends to lead to severe cartilage and bone destruction, thereby resulting in joint pain and arthritis [51]. Persistent joint inflammation can lead to cartilage and bone damage, joint damage, and even disability if the patients receive treatment not in time [52]. The pathogenesis of RA is complex and has not been fully elucidated [53]. Genetic susceptibility contributes to the increased prevalence of RA pathogenesis [54]. Epigenetic factors, such as DNA methylation and histone acetylation play a key role in RA [55]. The production of autoantibodies and the presence of autoreactive T cells in blood and synovial structures are distinguishing features of RA [56].

Studies have shown that RA is a potentially pathogenic effect of low appendicular lean mass and low grip strength [49]. The injury of RA to skeletal muscle can accelerate the occurrence of sarcopenia and seriously affect the life quality of patients [57,58]. Li et al [59] pointed out that the prevalence of sarcopenia in patients with RA was 31%, which is much higher than that in people without RA. Another cross-sectional study of 388 patients with RA showed that 37.1% of the participants had sarcopenia (14.7% severe sarcopenia, 22.4% sarcopenia) and 49.0% had low muscle mass [60]. Even more importantly, the incidence of sarcopenia increases with the lastingness of RA progression [59,61]. It is worth noting that RA patients with a higher percentage of body fat are more likely to develop sarcopenia [62].

Chronic inflammation is closely related to muscle damage in RA [63]. RA primarily affects the joints, but the risk and susceptibility factors can also cause inflammation in mucosal sites such as the mouth, lungs, and intestines. These sites can be recognized by the adaptive immune system, which triggers an immune response with the help of antigen-presenting cells. This response occurs in secondary lymphoid tissues, resulting in the production of autoantibodies. Subsequently, activated stromal cells like fibroblast-like synovial cells, antigen-presenting cells, and macrophages (MΦ) produce various inflammatory cytokines, including interleukin (IL)-1, IL-2, IL-6, IL-8, IL-17, tumor necrosis factor-α (TNF-α),

IFNγ (interferon gamma), and others, which can cause local inflammation and damage [64]. Researchers indicated that skeletal muscle metabolic disorders might be the leading cause of RA combined with sarcopenia [10]. However, skeletal muscle metabolism disorders can lead to loss of skeletal muscle due to impaired muscle anabolism, excessive muscle catabolism, or a combination of both [65]. The ubiquitin-proteasome pathway is a key pathway to increase muscle proteolysis [62,63]. Excessive production of proinflammatory factors makes a significant contribution to the breakdown of muscle protein. Higher levels of TNF-α and IL-1β induced by RA condition could elevate the expression level of IGFBP-5, IGFBP-3, scroggin-1, and muscle ring finger protein-1 (MuRF-1) through regulating the ubiquitin-proteasome system, thereby leading to increased hydrolysis of myofibrillar and soluble proteins [65].

Additionally, it was found that the amount of body fat and the density of muscle were closely linked to disability and physical performance in patients with RA. Specifically, individuals with a higher percentage of body fat showed a stronger correlation with the development of sarcopenia in RA. Therefore, it is recommended that the focus be on reducing fat and improving muscle quality as effective approaches to alleviating the disability of patients with impaired physical functioning [62]. Exercise could increase muscle mass in patients with RA effectively, so physical inactivity might be another risk factor for the high prevalence of RA combined with sarcopenia [66].

Inflammatory Bowel Disease and Sarcopenia

IBD, which includes ulcerative colitis and Crohn disease, is a progressive immune-mediated bowel disease for which there is no effective therapy treatment currently [57,67]. The intestinal microecology of patients with IBD is disturbed, which triggers changes in host immune response and metabolism that subsequently promote inflammation. The inflammatory response to IBD is characterized by a sustained increase in the production of inflammatory cytokines by T cells (TNF-α, IL-6, IL-1b, etc) [68]. Increased IL-12/23 and IFN-c levels, mediated by T helper cell 1, are supposed to be major factors in the maintenance of inflammation in patients with Crohn disease [69]. But T helper cell 2-mediated IL-5 and IL-13 levels elevation is an important factor for inflammation in ulcerative colitis patients [70].

Chronic inflammation and malnutrition resulting from IBD contribute to the development of sarcopenia [71,72]. Sarcopenia is a common condition in IBD patients and it increases fatigue and decreased quality of life. According to a recent study, sarcopenia occurs in 52% of people with Crohn disease and 37% of people with ulcerative colitis [71]. Although the underlying mechanism of sarcopenia in IBD patients remains unclear, studies indicated that the gut-skeletal muscle axis sheds light on the pathophysiology of IBD-associated sarcopenia. This axis comprises specific mediators from the gut that activate signaling pathways for amyotrophic and antimuscular atrophy in skeletal muscle

cells [73]. The up-regulation of TNF-α, NF-κB (nuclear factor kappa-B), and JAK/STAT signaling pathways is an important factor in the pathogenesis of sarcopenia [74]. Studies have shown increased levels of proinflammatory factors such as TNF-α, IL-6, circulating lipopolysaccharide, antimyogenic mediators, and promyogenic mediators (myostatin and insulin-like growth factor-1) in IBD patients [75,76]. Both TNF-α and IL-6 can activate NF-κB, which induces transcription of components of the ubiquitin-proteasome proteolytic pathway, such as atrophic protein-1 and MuRF-1, triggering protein degradation [77]. In addition, NF-κB further enhances IL-6 expression, creating a vicious cycle of inflammation and muscle protein degradation [78]. Inhibiting myostatin and muscular dystrophy factors such as atrophin-1 and MuRF-1 and enhancing myogenic factors including MyoG (myogenin) and MyoD (myoblast determination) can improve muscle atrophy [79]. Notably, the JAK/STAT signaling pathway is highly involved in the pathogenesis of IBD [80], mediating the function of several inflammatory cytokines involved in intestinal inflammation, such as IL-2, IL-4, IL-6, IL-7, IL-9, IL-12, IL-15, IL-21, IL-23, and IFN-γ [81].

Malnutrition often occurs in patients with intestinal insufficiency and intestinal failure. Malabsorption of micronutrients and macronutrients resulting from malnutrition can cause changes in body composition and increase the risk of sarcopenia [82]. In general, dietary patterns would have a great influence on the gut microbiota structure and function of patients with inflammatory diseases. For instance, the Mediterranean diet is beneficial for IBD patients with reduced inflammation and improved immune function, but the Western diet has the opposite effect [83]. In addition, vitamin D is involved in regulating muscle cell proliferation, differentiation, and regeneration. Consistent with this, research has shown that vitamin D supplementation is expected to reduce the occurrence of sarcopenia in IBD patients [84]. The inability to maintain protein balance after meals can lead to a decrease in muscle mass in patients with Crohn disease, exacerbating the occurrence of sarcopenia [85].

Ethical Considerations

This study used exclusively publicly accessible deidentified datasets, ensuring the absence of personal identifiers or sensitive information. Therefore, no ethical approval or declaration was required per the journal's policy and institutional guidelines. Given the absence of secondary analysis involving pre-existing nonidentifiable data, the research maintained full alignment with the Declaration of Helsinki principles. Methodological rigor was further reinforced through strict adherence to ethical protocols outlined in the JMIR Editorial Policies for data governance, as well as compliance with internationally validated open-science frameworks for responsible data use.

Discussion

Sarcopenia is common in the 3 autoimmune diseases commented on in this manuscript, T1DM, RA, and IBD. The combination of autoimmune diseases and sarcopenia can result in a diminished life quality, long-term disease prognosis management, and impose a substantial financial burden. Thus, it is important to investigate the relationship between sarcopenia and autoimmune diseases. Essentially, perturbations within the immune microenvironment of patients with autoimmune disorders elicit fluctuations in the populations of immune cells and alterations in the expression patterns of relevant factors. These modifications subsequently disrupt the functional coherence of muscle regeneration signaling cascades, ultimately underlying the pathogenesis of sarcopenia (Figure 3).

Autoimmune diseases are closely associated with alterations in the immune microenvironment. Pathological interactions between T-cells and B-cells serve as the foundation for numerous autoimmune diseases [86]. For T1DM [87] and RA [88], disruption of T-cell and B-cell tolerance, along with the production of autoantibodies, typically precede the diagnosis of autoimmune diseases. T1DM is characterized as the pancreatic beta cells destroyed by the immune system, resulting in life-long use of exogenous insulin, which places a great burden on patients and medical resources [89]. Pancreatic β cell injury is primarily attributed to T cells while antigen-presenting B cells exacerbate this damage by presenting antigens to T cells [90]. Multiple pieces of evidence indicate that T cells play a pivotal role in driving autoimmune responses in RA, with an abundance of these cells observed within inflamed synovial membranes [91]. The intestinal environment is highly complex, and the immune system maintains the entire intestine's health [92]. Among various factors contributing to the balance of intestinal microbiota, B cells undergo activation and maturation to generate the largest population of plasma cells secreting immunoglobulin A within the human body, thereby promoting immune system homeostasis [93]. Additionally, Follicular helper T cells are enriched in several inflammatory conditions, particularly within the intestine where they exhibit higher levels compared with other tissues [94].

Muscle atrophy represents a significant contributor to sarcopenia development wherein immune cells play a vital role in muscle regeneration. Immune cells release key inflammatory mediators that regulate the muscle fiber microenvironment [95]. Early recruitment of neutrophils leads to robust nonspecific responses that further exacerbate muscle fiber and extracellular matrix injuries [96-98]. Neutrophils exacerbate cellular injury by releasing reactive oxygen species, which induce muscle fiber damage and increase extravasated vascular permeability [99]. Furthermore, neutrophils secrete proinflammatory cytokines IL-6, IL-1β, and TNF-α, promoting satellite cell proliferation while inhibiting differentiation [100]. Both IL-6 and reactive oxygen species have been demonstrated to cause mitochondrial dysfunction/damage and alterations in protein stability within muscle fibers [99,100].

Cytotoxic T lymphocytes exhibit similar functions to neutrophils during the early stages of injury response [101]. Additionally, neutrophils and cytotoxic T lymphocytes recruit inflammatory macrophages to aid in the phagocytosis of damaged tissue for clearance while releasing proinflammatory mediators that stimulate satellite cell and fibroblast proliferation and enhance vascular permeability

[102]. However, the investigation of their roles in patients with autoimmune diseases complicated by sarcopenia remains limited. It can be speculated that these disruptions within the skeletal muscle microenvironment may lead to increased loss of muscle mass and fibrosis, resulting in reduced muscle plasticity, weakness, and fatigue.

Figure 3. The potential mechanism of autoimmune diseases combined with sarcopenia. IBD: inflammatory bowel disease; IFN: interferon; IGF: insulin-like growth factor; IL: interleukin; JAK/STAT: Janus kinase/signal transducer and activator of transcription; RA: rheumatoid arthritis; T1DM: type 1 diabetes mellitus; TNF: tumor necrosis factor; UPS: ubiquitin proteasome system.
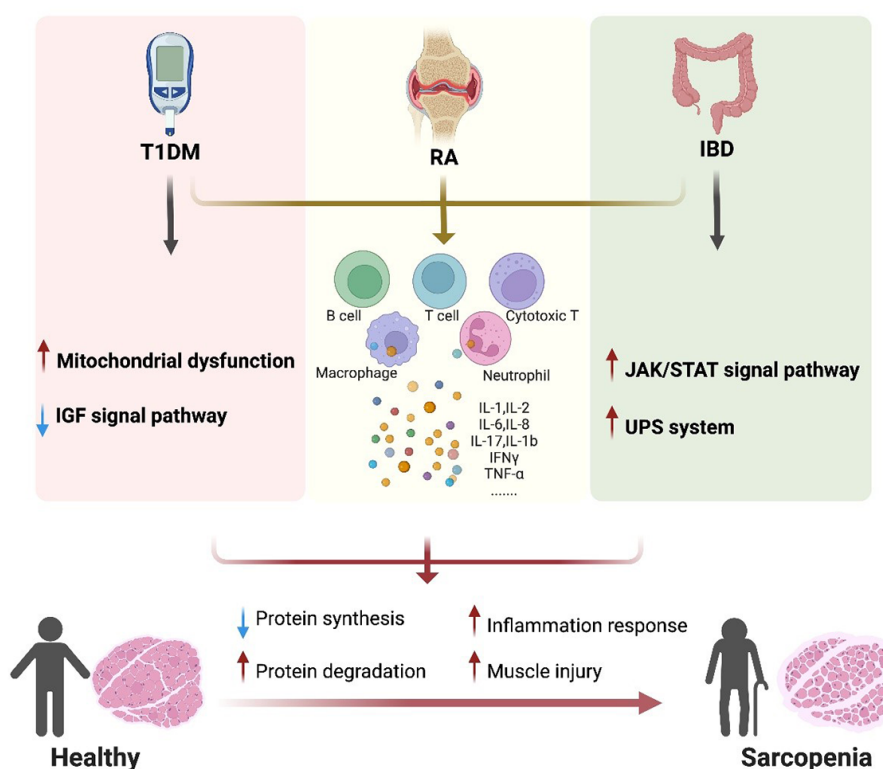
Conclusions

Autoimmune diseases are closely associated with alterations in the immune microenvironment which plays a crucial role in skeletal muscle differentiation and remodeling [103]. The pathogenesis of autoimmune diseases combined with sarcopenia can be attributed to an imbalance of hormones, growth factors, and proinflammatory factors in the immune microenvironment. This leads to muscle metabolism disorders resulting in a decline in muscle mass due to blocked muscle synthesis and excessive muscle catabolism. To mitigate

muscle loss, it is recommended to improve diet quality by consuming nutrients like vitamin D [104] and high-quality protein supplements [105]. Additionally, engaging in physical exercise may be an effective therapy to prevent autoimmune diseases combined with sarcopenia. However, there is still a lack of effective clinical treatment for these diseases, and the pathogenesis of autoimmune diseases combined with sarcopenia needs to be further elucidated [66,106,107]. Future research should focus on understanding the molecular mechanisms of various autoimmune diseases combined with sarcopenia and developing targeted therapies [108].

Authors' Contributions

Conflicts of Interest

None declared.

References

1. Chen LK, Woo J, Assantachai P, et al. Asian working group for sarcopenia: 2019 consensus update on sarcopenia diagnosis and treatment. J Am Med Dir Assoc. Mar 2020;21(3):300-307. [doi: 10.1016/j.jamda.2019.12.012] [Medline: 32033882]

2. Sayer AA, Cruz-Jentoft A. Sarcopenia definition, diagnosis and treatment: consensus is growing. Age Ageing. Oct 6, 2022;51(10):10. [doi: 10.1093/ageing/afac220]

3. Lipina C, Hundal HS. Lipid modulation of skeletal muscle mass and function. J Cachexia Sarcopenia Muscle. Apr 2017;8(2):190-201. [doi: 10.1002/jcsm.12144]

4. Kitamura A, Seino S, Abe T, et al. Sarcopenia: prevalence, associated factors, and the risk of mortality and disability in Japanese older adults. J Cachexia Sarcopenia Muscle. Feb 2021;12(1):30-38. [doi: 10.1002/jcsm.12651] [Medline: 33241660]

5. Ou Q, Pan D. Sarcopenia and risk of cardio-cerebrovascular disease: a two-sample Mendelian randomization study. BST. 2023;17(5):413-414. [doi: 10.5582/bst.2023.01246]

6. Eitmann S, Matrai P, Hegyi P, et al. Obesity paradox in older sarcopenic adults - a delay in aging: a systematic review and meta-analysis. Ageing Res Rev. Jan 2024;93:102164. [doi: 10.1016/j.arr.2023.102164] [Medline: 38103840]

7. Jones G, Trajanoska K, Santanasto AJ, et al. Genome-wide meta-analysis of muscle weakness identifies 15 susceptibility loci in older men and women. Nat Commun. ;12(1):654. [doi: 10.1038/s41467-021-20918-w]

8. Liu S, D'Amico D, Shankland E, et al. Effect of urolithin a supplementation on muscle endurance and mitochondrial health in older adults: a randomized clinical trial. JAMA Netw Open. Jan 4, 2022;5(1):e2144279. [doi: 10.1001/jamanetworkopen.2021.44279] [Medline: 35050355]

9. Tsuzuku S, Kajioka T, Sakakibara H, Shimaoka K. Slow movement resistance training using body weight improves muscle mass in the elderly: a randomized controlled trial. Scand J Med Sci Sports. Apr 2018;28(4):1339-1344. [doi: 10.1111/sms.13039] [Medline: 29247985]

10. Riuzzi F, Sorci G, Arcuri C, et al. Cellular and molecular mechanisms of sarcopenia: the S100B perspective. J Cachexia Sarcopenia Muscle. Dec 2018;9(7):1255-1268. [doi: 10.1002/jcsm.12363]

11. An HJ, Tizaoui K, Terrazzino S, et al. Sarcopenia in autoimmune and rheumatic diseases: a comprehensive review. Int J Mol Sci. Aug 7, 2020;21(16):16. [doi: 10.3390/ijms21165678] [Medline: 32784808]

12. Balestrieri P, Ribolsi M, Guarino MPL, Emerenziani S, Altomare A, Cicala M. Nutritional aspects in inflammatory bowel diseases. Nutrients. Jan 31, 2020;12(2):372. [doi: 10.3390/nu12020372] [Medline: 32023881]

13. Cruz-Jentoft AJ, Bahat G, Bauer J, et al. Sarcopenia: revised European consensus on definition and diagnosis. Age Ageing. Jan 1, 2019;48(1):16-31. [doi: 10.1093/ageing/afy169] [Medline: 30312372]

14. Vikberg S, Sörlén N, Brandén L, et al. Effects of resistance training on functional strength and muscle mass in 70-year-old individuals with pre-sarcopenia: a randomized controlled trial. J Am Med Dir Assoc. Jan 2019;20(1):28-34. [doi: 10.1016/j.jamda.2018.09.011]

15. Hua H, Xu X, Tang Y, Ren Z, Xu Q, Chen L. Effect of sarcopenia on clinical outcomes following digestive carcinoma surgery: a meta-analysis. Support Care Cancer. Jul 2019;27(7):2385-2394. [doi: 10.1007/s00520-019-04767-4]

16. Cho MR, Lee S, Song SK. A review of sarcopenia pathophysiology, diagnosis, treatment and future direction. J Korean Med Sci. May 9, 2022;37(18):e146. [doi: 10.3346/jkms.2022.37.e146] [Medline: 35535373]

17. Beaudart C, McCloskey E, Bruyère O, et al. Sarcopenia in daily practice: assessment and management. BMC Geriatr. Oct 5, 2016;16(1):170. [doi: 10.1186/s12877-016-0349-4] [Medline: 27716195]

18. Messina C, Maffi G, Vitale JA, Ulivieri FM, Guglielmi G, Sconfienza LM. Diagnostic imaging of osteoporosis and sarcopenia: a narrative review. Quant Imaging Med Surg. Feb 2018;8(1):86-99. [doi: 10.21037/qims.2018.01.01]

19. Mueller L, Mentil N, Staub N, et al. Association of thoracic skeletal muscle index with clinical outcome and response to nutritional interventions in patients at risk of malnutrition-secondary analysis of a randomized trial. Nutrients. Feb 5, 2023;15(4):817. [doi: 10.3390/nu15040817] [Medline: 36839175]

20. Mijnarends DM, Meijers JMM, Halfens RJG, et al. Validity and reliability of tools to measure muscle mass, strength, and physical performance in community-dwelling older people: a systematic review. J Am Med Dir Assoc. Mar 2013;14(3):170-178. [doi: 10.1016/j.jamda.2012.10.009] [Medline: 23276432]

21. Albano D, Messina C, Vitale J, Sconfienza LM. Imaging of sarcopenia: old evidence and new insights. Eur Radiol. Apr 2020;30(4):2199-2208. [doi: 10.1007/s00330-019-06573-2]

22. Kyle UG, Bosaeus I, De Lorenzo AD, et al. Bioelectrical impedance analysis--part I: review of principles and methods. Clin Nutr. Oct 2004;23(5):1226-1243. [doi: 10.1016/j.clnu.2004.06.004] [Medline: 15380917]

23. Gonzalez MC, Barbosa-Silva TG, Heymsfield SB. Bioelectrical impedance analysis in the assessment of sarcopenia. Curr Opin Clin Nutr Metab Care. Sep 2018;21(5):366-374. [doi: 10.1097/MCO.0000000000000496] [Medline: 29957677]

24. Bosaeus I, Wilcox G, Rothenberg E, Strauss BJ. Skeletal muscle mass in hospitalized elderly patients: comparison of measurements by single-frequency BIA and DXA. Clin Nutr. Jun 2014;33(3):426-431. [doi: 10.1016/j.clnu.2013.06.007]

25. Reiss J, Iglseder B, Kreutzer M, et al. Case finding for sarcopenia in geriatric inpatients: performance of bioimpedance analysis in comparison to dual x-ray absorptiometry. BMC Geriatr. Feb 29, 2016;16:52. [doi: 10.1186/s12877-016-0228-z] [Medline: 26928275]

26. Hacker UT, Hasenclever D, Baber R, et al. Modified Glasgow prognostic score (mGPS) is correlated with sarcopenia and dominates the prognostic role of baseline body composition parameters in advanced gastric and esophagogastric junction cancer patients undergoing first-line treatment from the phase III EXPAND trial. Ann Oncol. Jul 2022;33(7):685-692. [doi: 10.1016/j.annonc.2022.03.274] [Medline: 35395383]

27. Shivaji UN, Nardone OM, Cannatelli R, Smith SC, Ghosh S, Iacucci M. Small molecule oral targeted therapies in ulcerative colitis. Lancet Gastroenterol Hepatol. Sep 2020;5(9):850-861. [doi: 10.1016/S2468-1253(19)30414-5] [Medline: 32171056]

28. Wang CR, Tsai HW. Autoimmune liver diseases in systemic rheumatic diseases. World J Gastroenterol. Jun 21, 2022;28(23):2527-2545. [doi: 10.3748/wjg.v28.i23.2527] [Medline: 35949355]

29. Cao F, Liu YC, Ni QY, et al. Temporal trends in the prevalence of autoimmune diseases from 1990 to 2019. Autoimmun Rev. Aug 2023;22(8):103359. [doi: 10.1016/j.autrev.2023.103359] [Medline: 37201621]

30. Wang L, Wang FS, Gershwin ME. Human autoimmune diseases: a comprehensive update. J Intern Med. Oct 2015;278(4):369-395. [doi: 10.1111/joim.12395] [Medline: 26212387]

31. Miller FW. The increasing prevalence of autoimmunity and autoimmune diseases: an urgent call to action for improved understanding, diagnosis, treatment, and prevention. Curr Opin Immunol. Feb 2023;80:102266. [doi: 10.1016/j.coi.2022.102266]

32. Akil AAS, Yassin E, Al-Maraghi A, Aliyev E, Al-Malki K, Fakhro KA. Diagnosis and treatment of type 1 diabetes at the dawn of the personalized medicine era. J Transl Med. Apr 1, 2021;19(1):137. [doi: 10.1186/s12967-021-02778-6] [Medline: 33794915]

33. Wu D, Luo Y, Li T, et al. Systemic complications of rheumatoid arthritis: focus on pathogenesis and treatment. Front Immunol. 2022;13:1051082. [doi: 10.3389/fimmu.2022.1051082]

34. Singh N, Bernstein CN. Environmental risk factors for inflammatory bowel disease. UEG Journal. Dec 2022;10(10):1047-1053. [doi: 10.1002/ueg2.12319]

35. Massironi S, Viganò C, Palermo A, et al. Inflammation and malnutrition in inflammatory bowel disease. Lancet Gastroenterol Hepatol. Jun 2023;8(6):579-590. [doi: 10.1016/S2468-1253(23)00011-0]

36. Argollo M, Gilardi D, Peyrin-Biroulet C, Chabot JF, Peyrin-Biroulet L, Danese S. Comorbidities in inflammatory bowel disease: a call for action. Lancet Gastroenterol Hepatol. Aug 2019;4(8):643-654. [doi: 10.1016/S2468-1253(19)30173-6] [Medline: 31171484]

37. Cole JB, Florez JC. Genetics of diabetes mellitus and diabetes complications. Nat Rev Nephrol. Jul 2020;16(7):377-390. [doi: 10.1038/s41581-020-0278-5] [Medline: 32398868]

38. Figus FA, Piga M, Azzolin I, McConnell R, Iagnocco A. Rheumatoid arthritis: extra-articular manifestations and comorbidities. Autoimmun Rev. Apr 2021;20(4):102776. [doi: 10.1016/j.autrev.2021.102776] [Medline: 33609792]

39. Herold KC, Delong T, Perdigoto AL, Biru N, Brusko TM, Walker LSK. The immunology of type 1 diabetes. Nat Rev Immunol. Jun 2024;24(6):435-451. [doi: 10.1038/s41577-023-00985-4]

40. Eizirik DL, Pasquali L, Cnop M. Pancreatic β-cells in type 1 and type 2 diabetes mellitus: different pathways to failure. Nat Rev Endocrinol. Jul 2020;16(7):349-362. [doi: 10.1038/s41574-020-0355-7] [Medline: 32398822]

41. Sadeghi M, Dehnavi S, Jamialahmadi T, Johnston TP, Sahebkar A. Neutrophil extracellular trap: a key player in the pathogenesis of autoimmune diseases. Int Immunopharmacol. Mar 2023;116:109843. [doi: 10.1016/j.intimp.2023.109843] [Medline: 36764274]

42. Maratova K, Soucek O, Matyskova J, et al. Muscle functions and bone strength are impaired in adolescents with type 1 diabetes. Bone. Jan 2018;106:22-27. [doi: 10.1016/j.bone.2017.10.005]

43.   Mori H, Kuroda A, Yoshida S, et al. High prevalence and clinical impact of dynapenia and sarcopenia in Japanese patients with type 1 and type 2 diabetes: findings from the impact of diabetes mellitus on dynapenia study. J of Diabetes Invest. Jun 2021;12(6):1050-1059. [doi: 10.1111/jdi.13436]

44.   Sylow L, Tokarz VL, Richter EA, Klip A. The many actions of insulin in skeletal muscle, the paramount tissue determining glycemia. Cell Metab. Apr 6, 2021;33(4):758-780. [doi: 10.1016/j.cmet.2021.03.020] [Medline: 33826918]

45.   Hiromine Y, Noso S, Rakugi H, et al. Poor glycemic control rather than types of diabetes is a risk factor for sarcopenia in diabetes mellitus: the MUSCLES-DM study. J of Diabetes Invest. Nov 2022;13(11):1881-1888. [doi: 10.1111/jdi.13882]

46.   Shapiro MR, Wasserfall CH, McGrail SM, et al. Insulin-like growth factor dysregulation both preceding and following type 1 diabetes diagnosis. Diabetes. Mar 1, 2020;69(3):413-423. [doi: 10.2337/db19-0942]

47.   Hata S, Mori H, Yasuda T, et al. A low serum IGF-1 is correlated with sarcopenia in subjects with type 1 diabetes mellitus: findings from a post-hoc analysis of the iDIAMOND study. Diabetes Res Clin Pract. Sep 2021;179:108998. [doi: 10.1016/j.diabres.2021.108998] [Medline: 34390761]

48.   Perrini S, Laviola L, Carreira MC, Cignarelli A, Natalicchio A, Giorgino F. The GH/IGF1 axis and signaling pathways in the muscle and bone: mechanisms underlying age-related skeletal muscle wasting and osteoporosis. J Endocrinol. Jun 2010;205(3):201-210. [doi: 10.1677/JOE-09-0431] [Medline: 20197302]

49.   Schiaffino S, Mammucari C. Regulation of skeletal muscle growth by the IGF1-Akt/PKB pathway: insights from genetic models. Skelet Muscle. Jan 24, 2011;1(1):4. [doi: 10.1186/2044-5040-1-4] [Medline: 21798082]

50.   Alway SE. Mitochondrial dysfunction: linking type 1 diabetes and sarcopenia. Exerc Sport Sci Rev. Apr 2019;47(2):63. [doi: 10.1249/JES.0000000000000186] [Medline: 30882453]

51.   Krainer J, Siebenhandl S, Weinhäusel A. Systemic autoinflammatory diseases. J Autoimmun. May 2020;109:102421. [doi: 10.1016/j.jaut.2020.102421] [Medline: 32019685]

52.   Pietschmann P, Butylina M, Kerschan-Schindl K, Sipos W. Mechanisms of systemic osteoporosis in rheumatoid arthritis. Int J Mol Sci. Aug 5, 2022;23(15):15. [doi: 10.3390/ijms23158740] [Medline: 35955873]

53.   Gravallese EM, Firestein GS. Rheumatoid arthritis - common origins, divergent mechanisms. N Engl J Med. Feb 9, 2023;388(6):529-542. [doi: 10.1056/NEJMra2103726] [Medline: 36780677]

54.   Hemminki K, Li X, Sundquist J, Sundquist K. Familial associations of rheumatoid arthritis with autoimmune diseases and related conditions. Arthritis Rheum. Mar 2009;60(3):661-668. [doi: 10.1002/art.24328] [Medline: 19248111]

55.   Nemtsova MV, Zaletaev DV, Bure IV, et al. Epigenetic changes in the pathogenesis of rheumatoid arthritis. Front Genet. 2019;10:570. [doi: 10.3389/fgene.2019.00570] [Medline: 31258550]

56.   Di Matteo A, Bathon JM, Emery P. Rheumatoid arthritis. Lancet. Nov 25, 2023;402(10416):2019-2033. [doi: 10.1016/S0140-6736(23)01525-8] [Medline: 38240831]

57.   Bennett JL, Pratt AG, Dodds R, Sayer AA, Isaacs JD. Rheumatoid sarcopenia: loss of skeletal muscle strength and mass in rheumatoid arthritis. Nat Rev Rheumatol. Apr 2023;19(4):239-251. [doi: 10.1038/s41584-023-00921-9] [Medline: 36801919]

58.   Fukuda W, Omoto A, Ohta T, et al. Low body mass index is associated with impaired quality of life in patients with rheumatoid arthritis. Int J Rheum Dis. Jun 2013;16(3):297-302. [doi: 10.1111/1756-185X.12079] [Medline: 23981751]

59.   Li TH, Chang YS, Liu CW, et al. The prevalence and risk factors of sarcopenia in rheumatoid arthritis patients: a systematic review and meta-regression analysis. Semin Arthritis Rheum. Feb 2021;51(1):236-245. [doi: 10.1016/j.semarthrit.2020.10.002] [Medline: 33385864]

60.   Torii M, Hashimoto M, Hanai A, et al. Prevalence and factors associated with sarcopenia in patients with rheumatoid arthritis. Mod Rheumatol. Jul 2019;29(4):589-595. [doi: 10.1080/14397595.2018.1510565] [Medline: 30092163]

61.   Dietzel R, Wiegmann S, Borucki D, et al. Prevalence of sarcopenia in patients with rheumatoid arthritis using the revised EWGSOP2 and the FNIH definition. RMD Open. Sep 2022;8(2):2. [doi: 10.1136/rmdopen-2022-002600] [Medline: 36180102]

62.   Vlietstra L, Stebbings S, Meredith-Jones K, Abbott JH, Treharne GJ, Waters DL. Sarcopenia in osteoarthritis and rheumatoid arthritis: the association with self-reported fatigue, physical function and obesity. PLoS ONE. 2019;14(6):e0217462. [doi: 10.1371/journal.pone.0217462] [Medline: 31170172]

63.   Andonian BJ, Huffman KM. Skeletal muscle disease in rheumatoid arthritis: the center of cardiometabolic comorbidities? Curr Opin Rheumatol. May 2020;32(3):297-306. [doi: 10.1097/BOR.0000000000000697] [Medline: 32141950]

64.   Smolen JS, Aletaha D, Barton A, et al. Rheumatoid arthritis. Nat Rev Dis Primers. Feb 8, 2018;4:18001. [doi: 10.1038/nrdp.2018.1] [Medline: 29417936]

65. Castillero E, Martín AI, López-Menduiña M, Granado M, Villanúa MA, López-Calderón A. IGF-I system, atrogenes and myogenic regulatory factors in arthritis induced muscle wasting. Mol Cell Endocrinol. Oct 15, 2009;309(1-2):8-16. [doi: 10.1016/j.mce.2009.05.017] [Medline: 19501629]

66. Liao CD, Chen HC, Huang SW, Liou TH. Exercise therapy for sarcopenia in rheumatoid arthritis: a meta-analysis and meta-regression of randomized controlled trials. Clin Rehabil. Feb 2022;36(2):145-157. [doi: 10.1177/02692155211035539] [Medline: 34404254]

67. Chazaud B. Inflammation and skeletal muscle regeneration: leave it to the macrophages! Trends Immunol. Jun 2020;41(6):481-492. [doi: 10.1016/j.it.2020.04.006] [Medline: 32362490]

68. Boirivant M, Cossu A. Inflammatory bowel disease. Oral Dis. Jan 2012;18(1):1-15. [doi: 10.1111/j.1601-0825.2011.01811.x] [Medline: 21564424]

69. Fuss IJ, Heller F, Boirivant M, et al. Nonclassical CD1d-restricted NK T cells that produce IL-13 characterize an atypical Th2 response in ulcerative colitis. J Clin Invest. May 2004;113(10):1490-1497. [doi: 10.1172/JCI19836] [Medline: 15146247]

70. Bouma G, Strober W. The immunological and genetic basis of inflammatory bowel disease. Nat Rev Immunol. Jul 2003;3(7):521-533. [doi: 10.1038/nri1132] [Medline: 12876555]

71. Dhaliwal A, Quinlan JI, Overthrow K, et al. Sarcopenia in inflammatory bowel disease: a narrative overview. Nutrients. Feb 17, 2021;13(2):656. [doi: 10.3390/nu13020656] [Medline: 33671473]

72. Steell L, Gray SR, Russell RK, et al. Pathogenesis of musculoskeletal deficits in children and adults with inflammatory bowel disease. Nutrients. Aug 23, 2021;13(8):2899. [doi: 10.3390/nu13082899] [Medline: 34445056]

73. Ehlers L, Bannert K, Rohde S, et al. Preclinical insights into the gut-skeletal muscle axis in chronic gastrointestinal diseases. J Cell Mol Med. Aug 2020;24(15):8304-8314. [doi: 10.1111/jcmm.15554] [Medline: 32628812]

74. Nardone OM, de Sire R, Petito V, et al. Inflammatory bowel diseases and sarcopenia: the role of inflammation and gut microbiota in the development of muscle failure. Front Immunol. 2021;12:694217. [doi: 10.3389/fimmu.2021.694217] [Medline: 34326845]

75. de Sire R, Rizzatti G, Ingravalle F, et al. Skeletal muscle-gut axis: emerging mechanisms of sarcopenia for intestinal and extra intestinal diseases. Minerva Gastroenterol Dietol. Dec 2018;64(4):351-362. [doi: 10.23736/S1121-421X.18.02511-4]

76. Bian AL, Hu HY, Rong YD, Wang J, Wang JX, Zhou XZ. A study on relationship between elderly sarcopenia and inflammatory factors IL-6 and TNF-α. Eur J Med Res. Jul 12, 2017;22(1):25. [doi: 10.1186/s40001-017-0266-9] [Medline: 28701179]

77. Lin SY, Chen WY, Lee FY, Huang CJ, Sheu WHH. Activation of ubiquitin-proteasome pathway is involved in skeletal muscle wasting in a rat model with biliary cirrhosis: potential role of TNF-alpha. Am J Physiol Endocrinol Metab. Mar 2005;288(3):E493-501. [doi: 10.1152/ajpendo.00186.2004] [Medline: 15522995]

78. Vella L, Caldow MK, Larsen AE, et al. Resistance exercise increases NF-ϰB activity in human skeletal muscle. Am J Physiol Regul Integr Comp Physiol. Mar 15, 2012;302(6):R667-73. [doi: 10.1152/ajpregu.00336.2011] [Medline: 22189669]

79. Hong Y, Lee JH, Jeong KW, Choi CS, Jun HS. Amelioration of muscle wasting by glucagon-like peptide-1 receptor agonist in muscle atrophy. J Cachexia Sarcopenia Muscle. Aug 2019;10(4):903-918. [doi: 10.1002/jcsm.12434] [Medline: 31020810]

80. Olivera PA, Lasa JS, Bonovas S, Danese S, Peyrin-Biroulet L. Safety of janus kinase inhibitors in patients with inflammatory bowel diseases or other immune-mediated diseases: a systematic review and meta-analysis. Gastroenterology. May 2020;158(6):1554-1573. [doi: 10.1053/j.gastro.2020.01.001] [Medline: 31926171]

81. Liu C, Liu N, Xia Y, Zhao Z, Xiao T, Li H. Osteoporosis and sarcopenia-related traits: a bi-directional Mendelian randomization study. Front Endocrinol (Lausanne). 2022;13:975647. [doi: 10.3389/fendo.2022.975647] [Medline: 36187130]

82. Skallerup A, Nygaard L, Olesen SS, Køhler M, Vinter-Jensen L, Rasmussen HH. The prevalence of sarcopenia is markedly increased in patients with intestinal failure and associates with several risk factors. Clin Nutr. Dec 2018;37(6 Pt A):2029-2035. [doi: 10.1016/j.clnu.2017.09.010] [Medline: 29029893]

83. Aziz T, Khan AA, Tzora A, Voidarou CC, Skoufos I. Dietary implications of the bidirectional relationship between the gut microflora and inflammatory diseases with special emphasis on irritable bowel disease: current and future perspective. Nutrients. Jun 29, 2023;15(13):2956. [doi: 10.3390/nu15132956] [Medline: 37447285]

84. Palmese F, Del Toro R, Di Marzio G, Cataleta P, Sama MG, Domenicali M. Sarcopenia and vitamin D deficiency in patients with Crohn's disease: pathological conditions that should be linked together. Nutrients. Apr 20, 2021;13(4):1378. [doi: 10.3390/nu13041378]

85. Pizzoferrato M, de Sire R, Ingravalle F, et al. Characterization of sarcopenia in an IBD population attending an Italian gastroenterology tertiary center. Nutrients. Sep 24, 2019;11(10):2281. [doi: 10.3390/nu11102281] [Medline: 31554166]

86. Marks KE, Rao DA. T peripheral helper cells in autoimmune diseases. Immunol Rev. May 2022;307(1):191-202. [doi: 10.1111/imr.13069] [Medline: 35103314]

87. Sosenko JM, Skyler JS, Herold KC, Palmer JP, Type 1 Diabetes TrialNet and Diabetes Prevention Trial–Type 1 Study Groups. The metabolic progression to type 1 diabetes as indicated by serial oral glucose tolerance testing in the diabetes prevention trial-type 1. Diabetes. Jun 2012;61(6):1331-1337. [doi: 10.2337/db11-1660] [Medline: 22618768]

88. Nielen MMJ, van Schaardenburg D, Reesink HW, et al. Specific autoantibodies precede the symptoms of rheumatoid arthritis: a study of serial measurements in blood donors. Arthritis & Rheumatism. Feb 2004;50(2):380-386. [doi: 10.1002/art.20018]

89. Jeker LT, Bour-Jordan H, Bluestone JA. Breakdown in peripheral tolerance in type 1 diabetes in mice and humans. Cold Spring Harb Perspect Med. Mar 2012;2(3):a007807. [doi: 10.1101/cshperspect.a007807] [Medline: 22393537]

90. Smith MJ, Simmons KM, Cambier JC. B cells in type 1 diabetes mellitus and diabetic kidney disease. Nat Rev Nephrol. Oct 17, 2017;13(11):712-720. [doi: 10.1038/nrneph.2017.138] [Medline: 29038537]

91. Diogo D, Okada Y, Plenge RM. Genome-wide association studies to advance our understanding of critical cell types and pathways in rheumatoid arthritis: recent findings and challenges. Curr Opin Rheumatol. Jan 2014;26(1):85-92. [doi: 10.1097/BOR.0000000000000012] [Medline: 24276088]

92. Wastyk HC, Fragiadakis GK, Perelman D, et al. Gut-microbiota-targeted diets modulate human immune status. Cell. Aug 5, 2021;184(16):4137-4153. [doi: 10.1016/j.cell.2021.06.019] [Medline: 34256014]

93. Lundell AC, Björnsson V, Ljung A, et al. Infant B cell memory differentiation and early gut bacterial colonization. J Immunol. May 1, 2012;188(9):4315-4322. [doi: 10.4049/jimmunol.1103223] [Medline: 22490441]

94. Spencer J, Bemark M. Human intestinal B cells in inflammatory diseases. Nat Rev Gastroenterol Hepatol. Apr 2023;20(4):254-265. [doi: 10.1038/s41575-023-00755-6] [Medline: 36849542]

95. Tu H, Li YL. Inflammation balance in skeletal muscle damage and repair. Front Immunol. 2023;14:1133355. [doi: 10.3389/fimmu.2023.1133355] [Medline: 36776867]

96. Stackowicz J, Jönsson F, Reber LL. Mouse models and tools for the in vivo study of neutrophils. Front Immunol. 2019;10:3130. [doi: 10.3389/fimmu.2019.03130]

97. Xiao Y, Cheng Y, Liu WJ, et al. Effects of neutrophil fate on inflammation. Inflamm Res. Dec 2023;72(12):2237-2248. [doi: 10.1007/s00011-023-01811-2] [Medline: 37925664]

98. Singhal A, Kumar S. Neutrophil and remnant clearance in immunity and inflammation. Immunology. Jan 2022;165(1):22-43. [doi: 10.1111/imm.13423] [Medline: 34704249]

99. Kolaczkowska E, Kubes P. Neutrophil recruitment and function in health and inflammation. Nat Rev Immunol. Mar 2013;13(3):159-175. [doi: 10.1038/nri3399] [Medline: 23435331]

100. Mayadas TN, Cullere X, Lowell CA. The multifaceted functions of neutrophils. Annu Rev Pathol. 2014;9:181-218. [doi: 10.1146/annurev-pathol-020712-164023] [Medline: 24050624]

101. Deyhle MR, Hyldahl RD. The role of T lymphocytes in skeletal muscle repair from traumatic and contraction-induced injury. Front Physiol. 2018;9:768. [doi: 10.3389/fphys.2018.00768] [Medline: 29973887]

102. VanderVeen BN, Murphy EA, Carson JA. The impact of immune cells on the skeletal muscle microenvironment during cancer cachexia. Front Physiol. 2020;11:1037. [doi: 10.3389/fphys.2020.01037] [Medline: 32982782]

103. Morgan J, Partridge T. Skeletal muscle in health and disease. Dis Model Mech. Feb 6, 2020;13(2):dmm042192. [doi: 10.1242/dmm.042192] [Medline: 32066552]

104. Alliband KH, Kozhevnikova SV, Parr T, Jethwa PH, Brameld JM. In vitro effects of biologically active vitamin D on myogenesis: a systematic review. Front Physiol. 2021;12:736708. [doi: 10.3389/fphys.2021.736708] [Medline: 34566700]

105. Ahmadi A, Eftekhari MH, Mazloom Z, et al. Fortified whey beverage for improving muscle mass in chronic obstructive pulmonary disease: a single-blind, randomized clinical trial. Respir Res. Aug 17, 2020;21(1):216. [doi: 10.1186/s12931-020-01466-1] [Medline: 32807165]

106. Mc Gettigan N, Allen K, Saeidi R, O' Toole A, Boland K. A systematic review of the effect of structured exercise on inflammation and body composition in inflammatory bowel disease. Int J Colorectal Dis. May 25, 2023;38(1):143. [doi: 10.1007/s00384-023-04437-2] [Medline: 37227593]

107. Harmer AR, Chisholm DJ, McKenna MJ, et al. Sprint training increases muscle oxidative metabolism during high-intensity exercise in patients with type 1 diabetes. Diabetes Care. Nov 2008;31(11):2097-2102. [doi: 10.2337/dc08-0329] [Medline: 18716051]

108. Pascual-Fernández J, Fernández-Montero A, Córdova-Martínez A, Pastor D, Martínez-Rodríguez A, Roche E. Sarcopenia: molecular pathways and potential targets for intervention. Int J Mol Sci. Nov 22, 2020;21(22):22. [doi: 10.3390/ijms21228844] [Medline: 33266508]

Abbreviations

BIA: bioelectrical impedance analysis

DXA: dual-energy x-ray absorptiometry
IBD: inflammatory bowel disease
IFNγ: interferon gamma
IGF: insulin-like growth factor
IGFBP: insulin-like growth factor–binding protein
IL: interleukin
JAK/STAT: Janus kinase/signal transducers and activators of transcription
MuRF-1: muscle ring finger protein-1
MyoD: myoblast determination
MyoG: myogenin
NF-ϰB: nuclear factor kappa-B
RA: rheumatoid arthritis
T1DM: type 1 diabetes mellitus
TNF-α: tumor necrosis factor-α