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Review

Sarcopenia

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ABSTRACT

Sarcopenia is defined as a combination of low muscle mass with low muscle function. The term was first used to designate the loss of muscle mass and performance associated with aging. Now, recognized causes of sarcopenia also include chronic disease, a physically inactive lifestyle, loss of mobility, and malnutrition. Sarcopenia should be differentiated from cachexia, which is characterized not only by low muscle mass but also by weight loss and anorexia. Sarcopenia results from complex and interdependent pathophysiological mechanisms that include aging, physical inactivity, neuromuscular compromise, resistance to postprandial anabolism, insulin resistance, lipotoxicity, endocrine factors, oxidative stress, mitochondrial dysfunction, and inflammation. The prevalence of sarcopenia ranges from 3% to 24% depending on the diagnostic criteria used and increases with age. Among patients with rheumatoid arthritis 20% to 30% have sarcopenia, which correlates with disease severity. Sarcopenia exacts a heavy toll of functional impairment, metabolic disorders, morbidity, mortality, and healthcare costs. Thus, the consequences of sarcopenia include disability, quality of life impairments, falls, osteoporosis, dyslipidemia, an increased cardiovascular risk, metabolic syndrome, and immunosuppression. The adverse effects of sarcopenia are particularly great in patients with a high fat mass, a condition known as sarcopenic obesity. The diagnosis of sarcopenia rests on muscle mass measurements and on functional tests that evaluate either muscle strength or physical performance (walking, balance). No specific biomarkers have been identified to date. The management of sarcopenia requires a multimodal approach combining a sufficient intake of high-quality protein and fatty acids, physical exercise, and antiinflammatory medications. Selective androgen receptor modulators and anti-myostatin antibodies are being evaluated as potential stimulators of muscle anabolism.

1. Definition

The term sarcopenia was initially used to designate age-related loss of muscle. However, the definition of sarcopenia now encompasses muscle loss related to chronic disease, physical inactivity or impaired mobility, and malnutrition. Although it has been suggested that age-related primary sarcopenia could be differentiated from secondary sarcopenia due to a chronic disease or loss of mobility [1], this distinction is difficult to make in everyday practice, as older patients often have multiple comorbidities. Sarcopenia is defined as loss of muscle mass combined with alterations in physical function and muscle quality. These last two characteristics are strongly associated with morbidity and mortality [2,3]. Sarcopenia has been recognized as a disease by the World Health Organization and included in the International Classification of Diseases (ICD code M62.8) [4].

Cachexia is a complex multifactorial condition characterized by increased catabolic activity during a severe chronic disease associated with high-grade inflammation. The manifestations of cachexia include weight loss with loss of muscle mass and, often, of fat mass; metabolic disorders; and anorexia [5]. This definition of cachexia, in which weight loss is the main criterion, is not met in several chronic diseases such as rheumatoid arthritis (RA), during which the fat mass remains unchanged or increases, thus potentially explaining the absence of weight loss despite the loss of muscle mass [6]. This clinical phenotype known as sarcopenic obesity implies a tight connection between muscle and fat tissue. Sarcopenic obesity plays a central role in muscle function and quality impairments and in the development of cardiometabolic and bone disorders.

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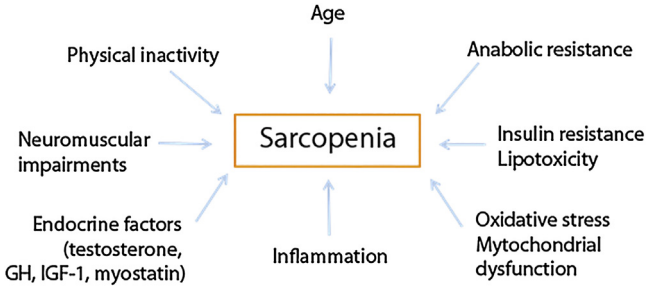

Fig. 1. Mechanisms underlying sarcopenia.

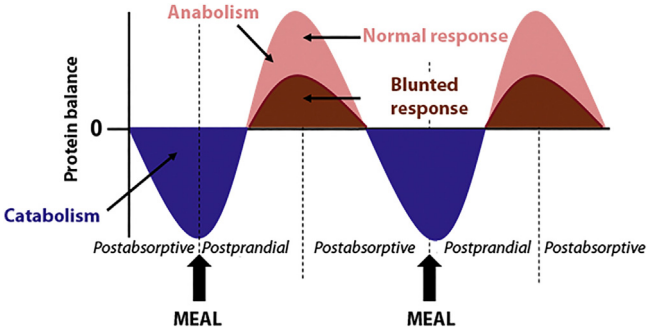

Fig. 2. The postprandial anabolic resistance concept: the postprandial anabolic peak pic is blunted in patients with anabolic resistance, resulting in a negative protein balance.

2. Mechanisms

The muscle is a biomechanical contractile organ that applies forces to bone, thereby allowing movement. In addition to this role in motricity, however, muscle is essential to metabolic homeostasis. Thus, muscle is a key player in glucose uptake, glycogen storage, lipid oxidation, amino acid release, and energy production. Furthermore, muscle is indirectly involved in the immune response, as it serves as a reservoir of amino acids that are rapidly available to immunocompetent cells. The mechanisms responsible for sarcopenia are complex and interdependent (Fig. 1).

2.1. Age, physical inactivity, neuromuscular impairments

Muscle mass declines with increasing age, chiefly at the expense of fast twitch type II fibers. The median annual decrease in muscle mass over the lifespan is 0.37% in females and 0.45% in males. Data on the age at which the decline begins are conflicting. However, after 70 years of age the annual decrease is 0.70% in females and 0.90% in males [7]. The age-related loss of muscle mass is due to a gradual decline in the synthesis of muscle proteins, including those present in the contractile apparatus and mitochondria, combined with impaired proteolysis control. The loss of strength (dynapenia) occurs at a 2- to 5-fold faster rate compared to the loss of muscle mass [7]. This finding suggests that the ability of muscle to generate force (muscle quality) may undergo early alterations due to changes in body composition and increases in fat mass [3].

Physical inactivity accelerates the loss of muscle mass and strength. During bed rest, 1 kg of muscle mass is lost after 10 days [8] and 9% of quadriceps strength after only 5 days, even in young individuals [9]. Neurological impairments that contribute to the loss of muscle include motor cortex atrophy, alterations in neurotransmitters, loss of fast twitch fibers leading to a predominance of slow twitch fibers, and loss of motor neurons responsible for motor unit loss and reorganization.

2.2. Postprandial resistance to anabolism

The decrease in the mass of muscle protein is the net result of an imbalance between protein synthesis (anabolism) and proteolysis (catabolism). Protein synthesis requires an adequate supply of amino acids from the diet or from proteolytic processes. Anabolism is triggered chiefly by the intracellular insulin signaling pathway and insulin-like growth factor-1 (IGF-1) receptor pathway (IGF-1/AKT/mTOR), which also inhibit proteolysis. Catabolism involves many specific proteolytic pathways, including the ATP-dependent ubiquitin-proteasome complex, which is influenced by multiple factors (inadequate nutrient intake, physical inactivity, hormone deficiencies, and proinflammatory cytokines). The main finding from studies on this topic is that aging is related, not to a basal disorder in protein renewal, but to a blunting of the anabolic response to food intake known as postprandial anabolic resistance (Fig. 2).

In the fasting state, the protein balance is negative, since protein synthesis falls below protein catabolism. In contrast, after a meal the protein balance normally becomes positive, as protein synthesis increases and proteolysis diminishes, particularly if the meal is high in protein. Aging is associated with impairments in the ability to synthesize protein in response to various nutritional factors (dietary protein, amino acids, insulin) [10]. In vitro, stimulation of rat muscle protein synthesis to a predefined level requires twice as much leucine in aged animals than in young animals [11]. The result is a negative protein balance with a steady decline in protein stores day after day.

2.3. Insulin resistance and lipotoxicity, endocrine factors

Insulin plays a major role in protein metabolism by stimulating amino acid transport within tissues, enhancing protein synthesis, and inhibiting proteolysis. However, the effects of insulin on muscle seem diminished during aging and in obese patients with insulin resistance [12,13]. Interestingly, muscle protein renewal correlates negatively with fat mass [13], suggesting an adverse effect of fat mass on muscle protein synthesis. The ectopic accumulation of toxic lipids (ceramides and diglycerides) within skeletal muscle promotes insulin resistance and muscle resistance to anabolism, a phenomenon known as muscle lipotoxicity [14]. In aged animals, adipose tissue expansion and, therefore, fatty acid uptake by adipose tissue are decreased, resulting in ectopic accumulation of toxic lipids within the muscle (myosteatosis) [14].

In addition to insulin, other hormones are involved in muscle mass loss, notably sex hormones (testosterone, dehydroepiandrosterone), cortisol, vitamin D, growth hormone (GH), IGF-1, and myostatin. These hormones act on the activation and proliferation of muscle satellite cells, adipogenesis, and proteolysis. However, the available data are fragmentary and difficult to reconcile given the wide variety of models and targets used in published studies.

3. Oxidative stress and mitochondrial dysfunction

Sarcopenia is associated with loss of muscle mitochondria and mitochondrial enzymes, mitochondrial DNA mutations and, eventually, alterations in fatty acid beta-oxidation and in the function of the mitochondrial respiratory chain that produces energy in the form of ATP. Together with impairments in cellular antioxidant properties, this age-related mitochondrial dysfunction contributes to the accumulation of reactive oxygen species (ROS), which alter the function of myofibrils, motor neurons, and the sarcoplasmic reticulum and impair muscle regeneration [7]. Increased ROS levels indicating exacerbated oxidative stress correlate with loss of handgrip strength in older women [7]. The decline in mitochondrial oxidative capacity can also promote lipid accumulation

Table 1
Criteria and cutoffs used to diagnose sarcopenia.

	EWGSOP	ESPEN SIG	IWGS	Sarcopenia with limited mobility	FNIH
Muscle mass					
DXA	SMI kg/m^2 ≤ 7.26 (M) ≤ 5.54 (F)	LM $_{total}$ kg	SMI kg/m^2 ≤ 7.23 (M) ≤ 5.67 (F)	SMI kg/m^2 ≤ 6.81 (M) ≤ 5.18 (F)	LM_{App} kg < 19.75 (M) < 15.02 (F) LM_{App} /BMI < 0.789 (M) < 0.512 (F)
Muscular function					
Handgrip	kg $_{BMI}$	–	–	–	< 26 kg (M) < 16 kg (F) kg/BMI < 1 (M) < 0.56 (F)
Walking speed	< 0.8 m/s	< 0.8 m/s	< 1 m/s	< 1 m/s 6MWT< 400 m	–
Timed get-up-and-go test	> 10 s	–	–	–	–

EWGSOP: European Working Group on Sarcopenia in Older People (Cruz-Jentoft et al., 2010); ESPEN SIG: Special Interest Group "cachexia-anorexia in chronic wasting diseases" (Muscaritoli et al., 2010); IWGS: International Working Group on Sarcopenia (Fielding et al., 2011); Sarcopenia with limited mobility: Society for Sarcopenia Cachexia and Wasting Disorders (Morley et al., 2011); FNIH Sarcopenia project (Studenski et al., 2014); LM: lean mass; App: appendicular; SMI: skeletal muscle mass index; BMI: body mass index; 6MWT: 6-minute walking test; M: male; F: female.

within skeletal muscle even when the dietary fat intake remains unchanged.

3.1. Inflammation

Elevated levels of C-reactive protein, IL-6, and TNFα may promote muscle loss and are associated in older individuals with declines in muscle mass and muscle strength [15]. IL-6 overexpression in transgenic mice induces muscle wasting, which can be reversed by administering an IL-6 receptor antagonist [16]. TNFα injection in mice activates the proteolytic pathways, notably those involving the proteasome, and impairs muscle function [17]. In patients with RA, IL-6 inhibition by tocilizumab is associated with lean mass gains, whereas fat mass does not increase [18]. The data on TNFα antagonists are less consistent [18].

A single study assessed the anabolic muscle response after meals and after exercise [19]. The patients had RA without sarcopenia. No differences were found with matched controls [19]. Insulin resistance is also associated with RA. Both proinflammatory cytokines (IL-6, TNFα) and glucocorticoids promote insulin resistance in RA [20]. Oxidative stress contributes to skeletal muscle dysfunction in animal models of collagen-induced arthritis [21]. Rats with collagen-induced arthritis exhibit protein metabolism alterations, fatty acid accumulation, and mitochondrial dysfunction, as well as muscle wasting, supporting the hypothesis that joint inflammation is associated with muscle lipotoxicity [22]. Among hormonal factors, myostatin is regulated during chronic inflammation and may therefore be involved in inflammatory sarcopenia via its catabolic effects [23].

4. Epidemiology and impact of sarcopenia on health

The prevalence of sarcopenia varies across populations and according to the definitions and cutoffs used. Prevalences of 3% to 24% have thus been reported in individuals older than 65 years [24] (Table 1). Using the criteria and cutoffs defined by the European Working Group on Sarcopenia in Older People (EWGSOP) [25], the prevalence is 7.1% when both loss of muscle mass and loss of muscle function are required and 11% when only the muscle mass loss criterion is required [24].

Sarcopenia has major adverse effects on function, metabolism, morbidity, and mortality. Thus, sarcopenia is associated with functional disabilities, quality of life impairments, falls, osteoporosis, dyslipidemia, an increased cardiovascular risk, metabolic syndrome, and immunosuppression. Both muscle mass and muscle function (strength, walking speed) are independently associated with mortality [2,26,27]. Decreases in both muscle mass and muscle function are associated with a 3.7-fold increase in mortality [26] and a 2-fold increase in the fall risk [24], as well as with a greater risk of dependency [28]. Sarcopenia is associated with a 50% increase in the risk of admission, a 20-day increase in hospital stay length, and a 34% to 58% increase in hospital care costs [29,30].

About 20% to 30% of patients with RA have a decrease in muscle mass [18,31]. Loss of muscle mass correlates with disease severity, disease activity, and quality of life [32–34]. Although loss of mobility is usually ascribed to the joint involvement, it explains only 20% of the decrease in walking speed. Body composition is the other major determinant [35]. The alterations in walking ability, quality of life, and self-sufficiency are even more marked in patients with sarcopenic obesity [28,34,35]. Changes in the ratio of lean mass over fat mass are probably also involved in the development of the cardiometabolic comorbidities seen in RA. Thus, a low body mass index (BMI) is associated with increases in the risks of cardiovascular disease [36] and metabolic syndrome, whereas the opposite is true in the general population [37]. That muscle, fat, and bone tissues are closely linked has been suggested for several years but remains controversial. In a prospective 3-year cohort study of 65-year-old retirees in Switzerland, sarcopenia was associated with a 2.3-fold increase in the risk of osteoporotic fracture after adjustment on age, gender, and the FRAX score [38]. Nevertheless, in a cohort of women in the US, bone mineral density (BMD) was the main determinant of the fracture risk, which was not increased by the presence of sarcopenia [39]. Muscle mass loss in patients with RA is associated with a BMD decrease at the hip but not with the fracture risk [40].

5. Diagnosis

The EWGSOP diagnostic criteria perform best in predicting the fall risk. Both muscle mass and muscle strength or physical performance must be measured [1,24,25] (Box 1).

Box 1
Criteria for the diagnosis of sarcopenia (EWGSOP)[a]

Low muscle mass Anthropometry Arm muscle area ≤ 21.4 cm^2 in males, ≤ 21.6 cm^2 in females Bioimpedance analysis SMI < 8.87 kg/m^2 in males, < 6.42 kg/m^2 in females FFMI ≤ 17 kg/m^2 in males, ≤ 15 kg/m^2 in females Computed tomography at L3 Lumbar SMI < 55 cm^2/m^2 in males, < 39 cm^2/m^2 in females Dual-energy X-ray absorptiometry (DXA) Appendicular SMI < 7.26 kg/m^2 in males, < 5.45 kg/m^2 in females
Low muscle strength Handgrip strength: varies with BMI and gender Males: BMI ≤ 24, 29 kg; 24 < BMI ≤ 28, 30 kg; BMI ≥ 29, 32 kg Females: BMI ≤ 23, 17 kg; 23 < BMI ≤ 26, 17.3 kg; 26 < BMI ≤ 29, 18 kg; BMI > 29, 21 kg
Low physical performance usual gait speed (< 0.8 m/s) timed get-up-and-go test > 10 s Short Physical Performance Battery (SPPB)

[a] EWGSOP defines sarcopenia as at least one muscle mass criterion plus at least one muscle strength or physical performance criterion. SMI: skeletal muscle mass index; FFMI: fat-free mass index.

Muscle mass can be estimated using a simple anthropometric method that consists in computing the corrected arm muscle area after measuring the triceps skinfold thickness [41]. Although few studies have assessed the performance and reproducibility of anthropometric methods, the corrected arm muscle area performed better than BMI in predicting mortality [41]. Bioimpedance analysis (BIA) is an inexpensive alternative to dual-energy X-ray absorptiometry (DXA) for obtaining an immediate measurement of lean mass but does not directly evaluate the muscle and bone compartments. BIA values vary with the degree of hydration of the individual, have not been validated in patients with chronic diseases, and underestimate lean mass. DXA is currently the investigation of reference for evaluating total body composition. DXA provides measurements of muscle mass, fat mass, and bone mass. DXA results can be used to compute the skeletal muscle mass index (SMI) by normalizing the lean mass of the four limbs to either height (in Europe) [1,25] or BMI (in the US) [42]. SMI cutoffs relative to a standard population have been determined for sarcopenia. Although DXA is the method of reference for accurately measuring body compartments and determining whether fat tissue is located in the subcutaneous or visceral compartment, it is a global, projected, two-dimensional technique that does not take into account any possible interactions among tissue types. Computed tomography (CT) of the lumbar spine with slices at the level of L3 followed by image analysis using dedicated software provides an estimate of lumbar skeletal muscle mass (psoas, rectus abdominis, external oblique, and paraspinal muscles). Peripheral quantitative CT (pQCT) is a more recently developed tool that is used in clinical research. With pQCT, three-dimensional transverse slices can be obtained at all four limbs and used to assess bone mass, muscle mass, and muscle density in the same volume.

Handgrip strength is used as a measure of muscle strength. Available tools for assessing physical performance include walking speed measurement, the step-on-stool test, or the Short Physical Performance Battery (SPPB) combining a measure of balance, walking speed, and the get-up-and-go test [25]. A sarcopenia screening questionnaire (SARC-F) can be helpful in patients older than 65 years [1].

A broad spectrum of phenotypes is associated with sarcopenia, ranging from loss of both muscle mass and fat mass (cachexia and pre-cachexia) to absence of weight loss or even weight gain (sarcopenic obesity). Criteria for evaluating the severity of sarcopenia have been developed [25]. Presarcopenia is characterized by low muscle mass that has no impact on muscle strength or physical performance. Sarcopenia is defined as low muscle mass combined with loss of muscle strength or physical performance. Severe sarcopenia is low muscle mass with both low muscle strength and low physical performance. Obesity or sarcopenic obesity can be defined as low muscle mass as assessed using DXA (SMI) combined with a fat mass greater than 28% in males and 40% in females. Sarcopenic obesity precedes and predicts loss of self-sufficiency, whereas neither obesity alone nor sarcopenia alone is independently associated with loss of self-sufficiency [28]. Nevertheless, these methods are neither readily available in everyday practice nor reimbursed by the French statutory health system. Furthermore, they do not allow a noninvasive or minimally invasive assessment of fatty infiltrates within muscle tissue [1,25]. This is regrettable, as muscle quality, which results from body composition, muscle function, and muscle fat content is a far better marker of both loss of mobility and mortality [3]. In oncology, muscle quality is recognized as a predictor of survival [43].

The complex and multifactorial pathophysiology of sarcopenia is a major obstacle to identifying a specific biomarker that would be easily available and would reflect both muscle mass and muscle function. The most widely cited markers reflect the level of inflammation and nutritional status (hemoglobin, albumin, CRP, IL-6, TNFα), oxidative stress (protein carbonylation, oxidized LDL), and hormonal status (testosterone, IGF-1, DHEA, vitamin D). None of these markers is specific of sarcopenia. The serum creatinine level reflects the muscle mass in individuals whose renal function is normal. A low serum creatinine level is associated with an increase in mortality [44]. Serum creatinine could be used in combination with another renal function marker, cystatin, to define a sarcopenia index [44]. Circulating free nucleic acids, procollagens, agrin, myokines, and proteomic parameters are being evaluated as biomarkers for sarcopenia.

6. Management of sarcopenia

A healthy diet and sufficient physical activity are the main determinants of energy homeostasis and body composition changes. Inflammation, insulin resistance, and physical inactivity promote fat deposition, anabolic resistance, and lipotoxicity within the sarcopenic muscle. Sarcopenia therefore requires a multimodal management approach combining a nutritional strategy targeting nutrient quality and intake, exercise, and antiinflammatory and anabolic medications.

6.1. Nutrition

In patients with age-related sarcopenia who are older than 65 years, the daily recommended protein intake is 1 to 1.2 g/kg/day instead of 0.8 g/kg/day [45]. Protein supplements, notably essential amino acid supplements including leucine may benefit muscle mass and function, although the benefits are inconsistent [46]. The rates of digestion and absorption, the modalities of protein intake throughout the day, and the synergistic effects of protein with physical exercise or other nutrients are key determinants of the effectiveness of the protein intake [47].

Vitamin D diminished lipotoxicity and exerted anabolic effects on muscle in animal studies [48]. In males older than 65 years, when used in combination with leucine-enriched whey protein for 6 weeks, vitamin D supplementation increased both postprandial protein synthesis and muscle mass [49]. Supplemental n-3 polyunsaturated fatty acids (omega-3) or monounsaturated fatty acids contributed to decrease insulin resistance and lipotoxicity [50]; prevented fat mass increases; and improved protein anabolism, muscle mass, and muscle function [51].

Appetite stimulants have been tested more specifically in patients with cachexia. Examples include megestrol acetate, a progestin medication, which can be given alone or with L-carnitine; thalidomide, and ghrelin.

6.2. Physical activity

Even low-level physical activity induces decreases in the cardiovascular risk, insulin resistance, and mortality [52,53]. Physical activity diminishes lipotoxicity by increasing mitochondrial fatty-acid beta-oxidation by muscle cells and increases the synthesis of muscle protein. Exercise benefits muscle strength and physical performance but does not consistently increase muscle mass [46]. The optimal exercise modalities and the patient subgroups most likely to benefit remain to be determined. Ideally, a physical training program should combine aerobic exercise to improve cardiovascular function and endurance and to decrease fat mass with strength exercises to increase muscle mass [54]. In RA, physical exercise programs should be individually tailored to disease stage, disease activity, and general health status. Intensive exercise programs designed to increase muscle mass and muscle strength

often raise difficulties with implementation and patient adherence.

6.3. Biotherapies

The metabolic effects of cytokine antagonists, notably on muscle anabolism, remain controversial and require further study. In several studies, TNFα antagonist or IL-6 antagonist therapy was associated with weight gain in patients with RA or spondyloarthritis (SpA). Although body composition changes have been documented in treated patients, few data are available on muscle strength and function, changes in energy expenditure and physical activity, and dietary intakes. The data should therefore be interpreted with caution. Body composition does not seem to change in the short term in patients with RA treated with TNFα antagonists, although an increase in fat mass has been reported after 2 years of treatment [55–57]. IL-6 antagonist therapy may hold promise for the treatment of cachexia in patients with cancer [58]. After 1 year of RA treatment with the IL-6 antagonist tocilizumab, patients had gained weight due to an increase in lean mass with no increase in fat mass but with a redistribution of adipose tissue toward the subcutaneous compartment [18]. In patients with SpA, TNFα antagonist therapy may increase the fat mass and induce redistribution of adipose tissue toward the visceral compartment [57,59].

6.4. Anabolic medications

Testosterone supplementation seems to have little efficacy in increasing muscle mass and is associated with adverse effects including cardiovascular events, prostate cancer, and virilization [60]. Selective androgen receptor modulators (SARMs) exert anabolic effects on bone and muscle but not on the other tissues. SARMs improved muscle mass and muscle function in phase II studies in older individuals and patients with cancer [61,62]. Phase II studies of SARMs are ongoing (NCT01355484). Estrogens have little effect, notably in women older than 60 years.

GH has produced disappointing effects in older patients. GH increases muscle mass but also induces salt and water retention and fails to improve muscle strength [63]. Creatine supplementation has controversial effects. When combined with physical exercise, creatine supplementation may improve both muscle mass and muscle strength [64]. Myostatin regulates muscle growth, and myostatin inhibition using a monoclonal antibody may constitute a targeted treatment for sarcopenia [65]. A single monthly subcutaneous injection of myostatin inhibitor improved muscle mass and decreased fat mass. Nevertheless, the effects on muscle function were discordant, and no improvements occurred in the 6-minute walking test, muscle strength, or the fall risk. Additional clinical trials are under way, notably with metformin (NCT02308228) and angiotensin-converting enzyme inhibitors (ISRCTN90094835) in combination with either physical activity or leucine supplementation.

7. Conclusion

The introduction of biotherapies that target the inflammatory processes underlying chronic inflammatory joint disease has constituted a therapeutic breakthrough. Nevertheless, both RA and SpA remain associated with a decline in physical capabilities and with numerous comorbidities responsible for both quality of life impairments and excess mortality. Body composition changes in these diseases, notably sarcopenic obesity, may contribute both to the functional disability and to the increased risk of comorbidities. Preserving or improving muscle mass and function is therefore a key goal to maintain function and improve quality of life in patients with chronic inflammatory joint disease. Achieving this goal will require investigations into the mechanisms underlying sarcopenia in patients with inflammatory conditions and reduced mobility. In addition, readily available and noninvasive biomarkers are needed to ensure the early identification of patients at high risk for sarcopenia. Treatment targets will need to be validated. Preventive and curative strategies combining nutrition optimization, physical activity, and long-term targeted medications will have to be developed. The recommendations and diagnostic tools discussed in this article apply to age-related sarcopenia. These data must now be validated in patients with chronic inflammatory joint disease in order to establish decision algorithms and clinical practice guidelines for identifying, preventing, or delaying the onset of sarcopenia.

Disclosure of interest

The authors declare that they have no competing interest.

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