REVIEW ARTICLE

Inflammation and age-associated skeletal muscle deterioration (sarcopaenia)

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Summary

Ageing is accompanied by chronic inflammatory responses due to elevated circulating inflammatory cytokine production. Several inflammatory cytokines have been shown to be responsible for a decrease in muscle mass. However, little is known about the possible relationship between inflammation and sarcopaenia. This review aims to summarise the existing evidence about inflammation and sarcopaenia. Sarcopaenia is defined as an age-related decrease of muscle mass and/or muscle strength; it is caused by multiple factors, such as skeletal muscle atrophy, neuromuscular junction degeneration, hormone imbalance, cytokine imbalance, protein synthesis and proteolysis. Several inflammatory cytokines have been considered to promote muscle loss; C-reactive protein levels are significantly upregulated in sarcopaenia and sarcopenic obesity, and high levels of interleukin-6 are associated with reduced muscle mass and muscle strength (the administration of interleukin-6 could lead to a reduction in muscle mass). Up-regulation of tumour necrosis factor-α expression is also related to the development of sarcopaenia. Signalling pathways, such as protein kinase B/mammalian target of rapamycin, Janus kinase/signal transducer and activator of transcription-5 and signal transducer and activator of transcription 3 signalling, involved in muscle metabolism are regulated by insulin-like growth factor-1, tumour necrosis factor-α and interleukin-6 respectively. In conclusion, the inflammatory cytokines produced during chronic inflammation due to ageing, may influence their respective related pathways, thus leading to age-related muscle deterioration.

The translational potential of this article: This review can provide more information for sarcopaenia medicine research in terms of anti-inflammation therapy.

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Introduction

Inflammation is now considered a major risk factor in age-related diseases, such as arthritis, osteoporosis, cardiovascular diseases and metabolic syndrome [1]. It is now accepted that chronic low-grade inflammation, which is quite different from acute inflammation, plays an important role in age-related diseases. Inflammatory cytokines are molecules that are secreted from immune cells and some other cell types, such as fibroblasts and endothelial cells, which are responsible for immune regulation [2]. Studies have shown that inflammatory cytokines accumulate during ageing and lead to a redox imbalance, which may act as the underlying mechanism in age-related diseases [3–5].

Aging has adverse effects on skeletal muscles. Sarcopenia is a syndrome characterised by progressive loss of skeletal muscle mass and strength, which can lead to physical disability and poor quality of life [6,7]. Age-related sarcopenia pathogenesis includes physical inactivity, malnutrition and increased oxidative stress [8]. Sarcopenia in the elderly has become a significant public health problem. It is reportedly associated with osteoporosis, and people with sarcopenia have higher fall risks than non-sarcopenic individuals [9,10]. Histologically, sarcopenia is characterised by fast-twitch type II muscle fibre atrophy and fatty infiltration, which is associated with muscle power loss [11].

It was recently demonstrated that inflammation is an important factor in sarcopenia. Circulatory cytokines participate in activating or blocking signalling pathways, thus affecting protein synthesis and proteolysis [12]. C-reactive protein, interleukin-6, tumour necrosis factor-α, growth hormone, interleukin-10 and interleukin-15 are considered to be related cytokines of sarcopenia according to the existing research [3–5]. However, there is no clearly defined relationship between inflammation and sarcopenia.

Therefore, this review aims to focus on the role of inflammatory cytokines and their corresponding molecular pathways that impact muscle metabolism in sarcopenia. We further describe the involvement of chronic inflammation in sarcopenia during ageing.

A literature search was performed in Pubmed (last access date was on 31 January 2017) using the following keyword search combination: "sarcopenic obesity OR sarcopenia OR low muscle mass OR low muscle strength" AND "inflammatory cytokine OR inflammatory marker OR inflammation". One thousand and thirty-six papers were retrieved in the initial search. From these results, 47 preclinical and clinical studies that investigated the relationship between inflammation and sarcopenia were included in this review. Thirteen additional studies that investigated signalling pathways involving the aforementioned cytokines related to sarcopenia were selected from the originally retrieved 1036 papers. Papers not written in English (approximately 4.2%) were excluded.

Pathogenesis of Sarcopenia

The progressive loss of muscle mass and strength due to ageing is considered to be attributed to complex interactive factors, such as neuromuscular junction degeneration, hormone imbalance, cytokine imbalance, protein synthesis and proteolysis [13,14]. Skeletal muscle atrophy due to ageing is mainly characterised by two factors: decreased cross-sectional area of individual muscle fibres and decreased number of muscle fibres. Both of these changes contribute to a decrease in muscle mass [15]. There is a reduction in the number of muscle neurons due to ageing, thus leading to progressive denervation of muscle fibres followed by partial re-innervation of remaining neurons. This is considered a crucial factor in age-related loss of muscle force [14–16]. In ageing individuals, there is a decline in the serum concentration of oestrogen, testosterone, growth hormone, dehydroepiandrosterone and insulin-like growth factor I (IGF-1). These anabolic hormones are associated with age-associated muscle loss [17,18]. As an individual ages, the balance of protein synthesis and degradation is disturbed: the rate of protein synthesis decreases but that of protein degradation increases. Even small imbalances of synthesis and proteolysis can eventually lead to sarcopenia [19].

C-Reactive Protein and Sarcopenia

C-reactive protein (CRP) is produced by the liver and is recognised as a marker of systemic inflammation. It can be triggered by cellular damage induced by injuries or disease, thus leading to inflammation [20]. High-sensitivity assays can detect CRP at very low concentrations.

In a study involving several thousand Eastern Europeans aged 65 years and older, CRP levels showed a significant increasing trend with ageing in the entire sample size (n = 3632, p = 0.003). In the subgroup of individuals who had age-related diseases/disability, CRP was not observed to increase with age (n = 2320, p = 0.249) [21]. It has been proven that CRP significantly positively-correlated (p < 0.01) with body mass index (BMI) (spearman correlation coefficient r_s = 0.34) and fat mass (r_s = 0.25) [22]. Atkins et al. reported that CRP levels were positively associated with low muscle mass independent of age, lifestyle and body composition [23]. Another study showed that high CRP (> 6.1 ng/mL) levels were associated with a 2- to 3-fold greater risk of losing more than 40% of muscle strength [24]. In clinical studies, patients with sarcopenia showed significantly higher CRP concentrations as compared to those without sarcopenia [25]. These studies have demonstrated that CRP levels are closely related to age-associated deterioration of skeletal muscle.

Sarcopenic obesity (SO) is defined as a combination of sarcopenia and obesity. It is characterised by excess weight, decreased muscle mass and/or decreased muscle strength [26]. Levine et al. investigated the changes of CRP levels in SO. In their study, CRP levels were highest in patients who were sarcopenic only, followed by the SO patients and non-sarcopenic obese patients, while those with normal body composition had the lowest CRP levels [27]. Similarly, Joppa et al. explored the relationship between inflammation and SO in Chronic Obstructive Pulmonary Disease (COPD) patients. The results demonstrated little difference from those in Levine’s study. They concluded that patients with SO had higher CRP levels than those with normal body composition. Moreover, patients with SO...
showed higher circulatory CRP levels than those with only sarcopenia [28]. Yang et al. conducted a community-based study and showed that high-sensitivity CRP (hs-CRP) levels were significantly higher in the obese only group and the SO group than in the normal group ($p = 0.012$ and 0.036, respectively), implying that SO is associated with increased hs-CRP levels [29]. In general, higher CRP levels are associated with SO; however, whether CRP is higher in SO patients than in those with only sarcopenia, remains uncertain. Van de Bool et al. investigated sarcopenia with or without abdominal obesity in COPD patients. They found that sarcopenic patients without abdominal obesity were younger and had lower CRP levels than sarcopenic patients with abdominal obesity [30]. Based on this evidence, it is apparent that CRP plays a crucial role in both primary and secondary sarcopenia, where circulatory CRP levels positively correlate with sarcopenia and sarcopenic obesity.

Higher levels of physical activity were consistently associated with 6–35% lower CRP levels when compared with lower levels of physical activity. Moreover, longitudinal training exercises reduced CRP concentrations by 16–41% [31]. However, another clinical study found no differences in CRP levels between the control and exercise groups [32]. Fedewa et al. analysed these inconsistent studies using meta-analysis. In their study, the mean effect size (ES) of 0.26 (95% confidence interval (CI) 0.18 to 0.34, $p < 0.001$) indicated a reduction of CRP levels after exercise. Exercise, when accompanied by a reduction in BMI, led to a greater decrease in CRP levels (ES = 0.38, 95% CI 0.26–0.50). These studies provide evidence that CRP levels decrease after exercise, which was consistent with the recommended interventions of sarcopenia by the European Working Group on Sarcopenia in Older People.

**Interleukin-6 and Sarcopenia**

Interleukin-6 (IL-6) is secreted by T cells, macrophages, fibroblasts and endothelial cells; it acts as a pro-inflammatory cytokine and an anti-inflammatory myokine. IL-6 was the first myokine to be identified and also the most frequently studied. It is considered a type of myokine, because circulatory IL-6 increases significantly during exercise. IL-6 acts through two different pathways. The first is the classic IL-6 signalling via membrane-bound receptors (IL-6R), which is mainly regenerative, protective and anti-inflammatory. Conversely, the second pathway via the soluble IL-6R (sIL-6R) is instead pro-inflammatory [33]. IL-6 is important for both specific and nonspecific immune responses. In acute-phase immune responses, IL-6 can induce the production of CRP, complement components and other acute-phase proteins [34]. Furthermore, IL-6 also induces differentiation of activated B cells, leading to the production of immunoglobulins [35,36].

It is indicated that IL-6 gene expression, serum concentrations and tissue levels all increase with age [37–39]. The age-related increase of IL-6 accounts for some alterations due to ageing, such as lean body mass decrease and bone mineral density (BMD) reduction [40], and thus, it very likely that it accounts for the age-associated skeletal muscle deterioration (sarcopaenia) and other alterations during ageing [40].

A study showed that increased levels of IL-6 was significantly associated with sarcopenia in elderly patients with renal disease (OR = 2.35, 95% CI: 1.21–4.58) [41]. Dutra et al. reported that IL-6 levels significantly positively-correlated ($p < 0.05$) with age ($r = 0.19$), fat mass ($r = 0.19$) and waist circumference ($r = 0.17$). Handgrip strength significantly decreased with higher IL-6 levels ($p = 0.02$) in this study [22]. Similarly, higher levels of IL-6 ($> 5$ pg/mL) were found to lead to an increased risk of loss of muscle mass and a reduction of muscle strength in the elderly [24]. Schaap et al. investigated a correlation between cytokine levels and sarcopenia, and confirmed that IL-6 levels were up-regulated in older persons, with an association between increased IL-6 soluble receptor levels and a decrease of muscle strength in men. As we now know, soluble receptor levels can mediate pro-inflammatory reactions; thus, the decline of muscle strength may be due to IL-6/sIL-6R signalling pathways. However, in a cross-sectional study on older men, IL-6 was not associated with mid-arm muscle circumference and fat-free mass index [23]. Based on the current evidence, it is believed that high levels of IL-6 are associated with low muscle mass and decreased muscle strength. This is substantiated by an in vivo study which showed that the administration of IL-6 could lead to muscle mass reduction [42].

Joppa et al. reported that patients with SO presented with higher IL-6 levels ($p < 0.01$) than those with only sarcopenia. Compared with the patients with normal body composition, those with SO were shown to have higher IL-6 levels ($p < 0.01$) [28]. Research on inflammation and obesity using logistic regression analysis indicated a greater possibility of metabolically healthy obesity with lower IL-6 concentrations (odds ratios (ORs), 1.7–2.9) among individuals [43]. Another report showed that obese individuals (BMI ≥ 30 kg/m²) presented with significantly increased hypermethylation of the IL-6 gene compared to individuals with normal weight (BMI < 23 kg/m²) and those who were overweight (BMI = 23–30 kg/m²) (p = 0.034 and 0.026, respectively), implying that methylation of the IL-6 gene may be one of the mechanisms in sarcopenic obesity [44]. Therefore, the expression of the IL-6 gene increases in SO patients, particularly in unhealthy obese individuals.

The level of plasma IL-6 was significantly greater after high-intensity interval exercise (2.70 ± 1.51) than after low-intensity interval exercise (1.40 ± 0.32) (p = 0.04), suggesting that exercise could result in a significant increase of IL-6 levels, and that the increase was greater in the high-intensity group than in the low-intensity group [45]. However, another study on postmenopausal women showed inconsistent results. After endurance exercise, a decline of IL-6 levels were detected and the decline was parallel with improvements of the metabolic syndrome score ($r = 0.30, p = 0.04$); in addition, high-density lipoprotein cholesterol levels ($r = -0.33, p = 0.03$) improved in the exercise group. These changes demonstrate the beneficial effects of exercise on high-density lipoprotein cholesterol levels and low-grade inflammatory states [46]. Therefore, more studies are needed to evaluate the change of IL-6 during and after exercise to unravel the relationship between IL-6 and exercise, as well as the role of IL-6 (pro-inflammation or anti-inflammation) during exercise. Only after understanding
the mechanism and role of IL-6 during exercise can we develop clinical applications for sarcopenia.

Tumour Necrosis Factor-α and Sarcopenia

Tumour necrosis factor (TNF) was named so, because it was first identified as responsible for the haemorrhagic necrosis of tumours. It is mainly secreted by macrophages. The concentration of plasma TNF-α was significantly more elevated in aged individuals than in middle-aged subjects, implying that inflammatory biomarkers increased gradually with age [47]. TNF is considered to be a pro-inflammatory cytokine related to the wasting syndrome in many chronic diseases, such as chronic infection. TNF-α (a member of the TNF superfamily), also called cachectin, is a protein responsible for metabolic disorders, such as chronic inflammation, accompanied with IL-1 formation. An in vitro study reported that TNF-α had positive effects on IL-6 secretion from skeletal cells [48]. IL-1 and IL-6 both play important roles in inflammatory responses and the immune system [49,50].

TNF-α has been regarded as a crucial factor in the loss of muscle mass and muscle damage. It can induce muscle loss by promoting protein degradation and decreasing protein synthesis [51,52]. Wang et al. has confirmed that the increase of TNF-α could accelerate catabolic pathways in skeletal muscle [53]. It is believed that the up-regulation of TNF-α may lead to muscle proteolysis, which subsequently causes a decrease in muscle mass and eventually sarcopenia. One of the reasons may be that TNF-α induces both type I and type II muscle fibre apoptosis [54]. Furthermore, a report showed that TNF-α inhibited myogenic differentiation through MyoD protein destabilisation [55]. Two clinical studies in community-dwelling elderly provided more evidence of the same. (1) A previous study in older persons showed that higher levels of TNF-α were associated with a decline in thigh muscle cross-sectional area and hand grip strength \( p = 0.02 \) and \( 0.03 \), respectively, suggesting that TNF-α was consistently associated with the decline of both muscle mass and muscle strength [56]. (2) Another study in frail elderly persons presented similar results; a significant negative correlation between protein synthesis and TNF-α levels was detected in the study [57].

Several previous studies investigated the role of TNF-α in skeletal muscle using different methods. Zamir et al. administered TNF-α injections in skeletal muscle and observed a significant increase in proteolysis and protein synthesis tended to decrease [58]. In another study, TNF inhibition therapy led to a significantly higher fat mass; however, no significant difference was found in muscle mass and muscle strength [59]. TNF-α gene transfer resulted in an elevated concentration of TNF-α and muscle atrophy in vivo; the regeneration of injured muscle was also significantly inhibited [60]. These studies indirectly prove that TNF-α is associated with catabolism of muscle protein.

The TNF-α gene is mapped to human chromosome 6 [61]. Polymorphism at –308 in the TNF-α promoter is associated with activation of TNF-α gene transcription [62]. Di et al. investigated the association between G/A –308 TNF-α polymorphism and skeletal muscle mass. They observed that SO was positively associated with –308 TNF-α polymorphism, suggesting that the TNF-α polymorphism accounted for SO susceptibility in normal weight obese (NWO) syndrome [63]. NWO syndrome is characterized by normal body mass index (BMI), but high amount of fat mass and reduced lean mass. However, a large-scale clinical study investigating the relationship among obesity, muscle strength and circulating pro-inflammatory cytokines, involving 378 men and 493 women aged ≥65 years, did not find any significant difference in TNF-α levels among no obesity group, central obesity group, global obesity group and both global and central obesity group, which may be due to the very low circulating levels and very short half-life of TNF-α [64].

Starkie et al. attempted to explore the relationship between exercise and TNF-α. They found that the administration of endotoxin induced a significant increase of plasma TNF-α \( (p < 0.0001) \) in the control group, but this increase was alleviated by physical exercise (riding a bicycle), and hence, there was no increase of the TNF-α level in the exercise group. This study suggests that exercise can inhibit TNF-α production, implying that TNF-α plays an anti-inflammatory role in exercising muscles [65]. Similarly, another study in frail elderly individuals revealed that the rate of muscle protein synthesis in the exercise group (resistance exercise) was negatively correlated with muscle TNF-α protein content \( r = -0.53, p = 0.04 \). These results provide evidence for TNF-α’s role in age-associated deterioration of skeletal muscle. Exercise can suppress TNF-α expression in skeletal muscle, which may retard muscle wasting [57]. In general, the up-regulation of TNF-α expression is regarded as one of the mechanisms in the development of sarcopenia, and TNF-α can also be a potential serum marker in individuals with sarcopenia.

Other Cytokines: Growth Hormone, Interleukin-10, Interleukin-15

Growth hormone (GH) is mainly secreted by somatotrophs in the anterior pituitary gland. It has been proven that the GH-IGF (insulin-like growth factors) axis regulates the growth and differentiation of skeletal muscles [66]. The GH-IGF axis is also crucial for the regulation of immunity and inflammation [67]. GH levels are usually lower in elderly people. Brioche et al. applied GH replacement therapy to aged rats and found an increased synthesis of skeletal muscle protein, suggesting that GH may have beneficial effects for the treatment of sarcopenia [68]. Another study has also found that GH secretion was suppressed in SO patients, which is usually accompanied by a decrease of IGF-1 [69]. Similarly, a significant negative correlation was observed between basal free fatty acid (FFA) levels and GH levels \( r = -0.44, p = 0.001 \), indicating that a decreased release of GH during ageing may be due to an increase of FFA [69,70]. These studies help us to understand that low GH levels were associated with low muscle mass. It is reported that exercise can increase GH secretion, suggesting that it can act as a stimulus for GH secretion in individuals [71].

IL-10 is mainly produced by monocytes and was reported to be increased in elderly people [72,73]. It is considered to
be an anti-inflammatory cytokine. IL-10 levels were upregulated during exercise, indicating that it may also be secreted by skeletal muscles [74]. Compared to age matched wild-type controls, skeletal muscles of IL-10 null mice presented with higher levels of damaged mitochondria and destructive autophagosomes, suggesting that IL-10 and inflammation were important in altered mitochondrial biology, in skeletal muscles of aged mice [75]. Additionally, circulatory IL-10 levels were elevated in obese individuals [76]. After 16 weeks of high-fat diet administration, muscle-specific overexpression of interleukin-10 (mL-10) mice developed obesity, but their insulin function was better than that of wild-type mice. This implies that IL-10 may be able to attenuate inflammation and improve insulin sensitivity in skeletal muscles of obese mice [77].

IL-15 is expressed in many cell types, including monocytes, macrophages and fibroblasts. It can facilitate satellite cell differentiation and regulate the balance between muscle cells and adipocytes [78]. Marzetti et al. found that ageing is associated with a reduction of IL-15 signalling in muscles and that calorie restriction can preserve IL-15 signalling, which may contribute to an anti-ageing effect, preventing muscle wasting in rats [79]. IL-15 was also reported to be significantly increased after resistance exercise and endurance exercise in clinical studies, suggesting that it may be a mediator of skeletal muscle mass [80,81]. IL-15 has therapeutic potential to reduce inflammation, thus alleviating muscle loss.

**Pathways Related to Inflammation in Sarcopaenia**

The signalling pathways involved in protein synthesis and degradation are very complicated and regulated by multiple factors. Inflammation and the related inflammatory cytokines are very likely to be involved in age-related muscle loss in humans.

Akt (known as protein kinase B, PKB)/mTOR (mammalian target of rapamycin) and Akt/GSK (glycogen synthase kinase) pathways are related to muscle protein synthesis, and the GH/IGF-1 axis is a key regulator within these pathways [82,83]. IGF-1 affects Akt activation, thus regulating the Akt/mTOR and Akt/GSK pathways [84]. IGF-1 was found to be decreased in older people, and so were the downstream regulators, such as mTOR, p70S6k and eIF2B [85,86]. Thus, these pathways may also contribute to decreased muscle protein synthesis during ageing. Akt/FKHR (forkhead family of transcription factors, also called Foxo1) and Akt/FKHRl1 (Foxo3) are the pathways responsible for muscle protein degradation. Reduction of Akt phosphorylation caused by a decrease of IGF-1 in the elderly could activate FKHR, thus promoting the transcription of atrogin-1 and MuRF1 (muscle ring-finger protein 1). These two genes are involved in muscle atrophy [87,88].

STAT3 (signal transducer and activator of transcription 3) is a downstream effector of IL-6. The IL-6-activated STAT3 signalling pathway can regulate satellite cell differentiation, thus facilitating myogenic differentiation. This indicates that IL-6 and its receptor could activate its downstream signalling pathways in skeletal muscle, under pathological conditions [89]. After treating muscle cells with myostatin, IL-6 levels were elevated through MEK1 (mitogen-activated protein kinase 1) and p38 MAPK pathways. This may be another mechanism related to protein degradation and age-related muscle loss [90]. Additionally, IL-6 was also involved in activating AMPK (adenosine monophosphate-activated protein kinase) and PI3K (phosphatidylinositol 3-kinases) pathways, thus regulating skeletal muscle metabolism [91,92].

TNF-α could increase myostatin expression through the NF-κB signalling pathway. In elderly people, there was a substantial increase of TNF-α, which led to the increase of its target gene SOCS-3 (suppressor of cytokine signalling 3) [93]. SOCS-3 could block the growth hormone receptor signalling pathway, thus resulting in the inhibition of JAK (Janus kinase)/STAT5 (signal transducer and activator of transcription-5) [94]. As JAK/STAT5 pathway is related to muscle protein synthesis, the indirect inhibition of this pathway by TNF-α would lead to a decrease of protein synthesis.

The summary of inflammatory cytokines related to sarcopaenia in this review are listed in Table 1.

The purpose of this review was to identify the most relevant and widely studied inflammatory factors related to the pathogenesis of sarcopaenia, with a high potential for being used in an interventional target strategy. However, limitations exist for some factors that were not as widely reported; these factors were not included in this review.

| Inflammatory cytokines | Source | Function | Tendency in sarcopaenia | Related pathways |
|------------------------|--------|----------|-------------------------|-----------------|
| CRP                    | Liver  | A marker of systemic inflammation | ↑ | STAT3; MEK1; p38 MAPK; AMPK; PI3K |
| IL-6                   | T cells, macrophages, fibroblasts and endothelial cells | A pro-inflammatory cytokine and an anti-inflammatory myokine | ↑ | NF-κB; JAK/STAT5 |
| TNF-α                  | Macrophages | A pro-inflammatory cytokine | ↑ | Akt/mTOR; Akt/GSK |
| GH                     | Somatotroph in anterior pituitary gland | GH/IGF axis regulates the growth and differentiation of skeletal muscles | ↓ | |
| IL-10                  | Monocytes | Anti-inflammatory cytokine | ↑ | |
| IL-15                  | Mononuclear phagocytes | Induces differentiation of NK cells and T cells | ↓ | |

CRP = C-reactive protein; GH-IGF = growth hormone-insulin-like growth factors; IL = interleukin; mTOR, mammalian target of rapamycin; TNF-α = tumour necrosis factor-α.
Moreover, as sarcopenia is a multifactorial disease, other important factors, including ageing, exercise, diet and their interactions, were not discussed in depth to avoid complication.

**Conclusion**

This review summarises the current evidence about inflammation and age-associated deterioration of skeletal muscle. CRP, IL-6, and TNF-α are crucial inflammatory cytokines associated with sarcopenia. All of which showed higher expression in elderly individuals. In conclusion, the cytokines produced during inflammatory processes related to ageing may influence their respective related pathways, thus leading to age-related muscle deterioration.

**Conflicts of interest**

The authors have no conflicts of interest relevant to this article.

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**References**

[1] Chung HY, Sung B, Jung KJ, Zou Y, Yu BP. The molecular inflammatory process in aging. Antioxid Redox Signal 2006;8:572–81.
[2] Zhang JM, An J. Cytokines, inflammation, and pain. Int Anesthesiol Clin 2007;45:27–37.
[3] Chung HY, Cesari M, Anton S, Marzetti E, Giovannini S, Seo AY, et al. Molecular inflammation: underpinnings of aging and age-related diseases. Ageing Res Rev 2009;8:8–30.
[4] Zou Y, Jung KJ, Kim JW, Yu BP, Chung HY. Alteration of soluble adhesion molecules during aging and their modulation by calorie restriction. FASEB J 2004;18:320–2.
[5] Bruinsgaard H. The clinical impact of systemic low-level inflammation in elderly populations. With special reference to cardiovascular disease, dementia and mortality. Dan Med Bull 2006;53:285–309.
[6] Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, et al. Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in older people. Age Ageing 2010;39:412–23.
[7] Cruz-Jentoft AJ, Landi F, Schneider SM, Zuniga C, Arai H, Boirie Y, et al. Prevalence of and interventions for sarcopenia in ageing adults: a systematic review. Report of the International Sarcopenia Initiative (EWGSOP and IWGS). Age Ageing 2014;43:748–59.
[8] Tarantino U, Piccirilli E, Fantini M, Baldi J, Gasbarra E, Bel R. Sarcopenia and fragility fractures: molecular and clinical evidence of the bone-muscle interaction. J Bone Joint Surg Am 2015;97:429–37.
[9] Landi F, Liperoti R, Russo A, Giovannini S, Tosato M, Capoluongo E, et al. Sarcopenia as a risk factor for falls in elderly individuals: results from the iSIRENTE study. Clin Nutr 2012;31:652–8.
[10] Yoshimura N, Muraki S, Oka H, Iidaka T, Kodama R, Kawaguchi H, et al. Is osteoporosis a predictor for future sarcopenia or vice versa? Four-year observations between the second and third ROAD study surveys. Osteoporos Int 2017;28:189–99.
[11] Budui SL, Rossi AP, Zamboni M. The pathogenetic bases of sarcopenia. Clin Cases Miner Bone Metab 2015;12:22–6.
[12] Jo E, Lee SR, Park BS, Kim JS. Potential mechanisms underlying the role of chronic inflammation in age-related muscle wasting. Aging Clin Exp Res 2012;24:412–22.
[13] Dhillon RJ, Hasni S. Pathogenesis and management of sarcopenia. Clin Geriatr Med 2017;33:17–26.
[14] Ryall JG, Schertzer JD, Lynch GS. Cellular and molecular mechanisms underlying age-related skeletal muscle wasting and weakness. Biogerontology 2008;9:213–28.
[15] Faulkner JA, Larkin LM, Claffin DR, Brooks SV. Age-related changes in the structure and function of skeletal muscles. Clin Exp Pharmacol Physiol 2007;34:1091–6.
[16] Xie Y, Yao Z, Chai H, Wong WM, Wu W. Expression and role of low-affinity nerve growth factor receptor (p75) in spinal motor neurons of aged rats following axonal injury. Dev Neurosci 2003;25:65–71.
[17] Solomon AM, Bouloux PM. Modifying muscle mass—the endocrine perspective. J Endocrinol 2006;191:349–60.
[18] Chahal HS, Drake WM. The endocrine system and ageing. J Pathol 2007;211:173–80.
[19] Mosoni L, Malmazet T, Valluy MC, Houlier ML, Attaix D, Mirand PP. Lower recovery of muscle protein lost during starvation in old rats despite a stimulation of protein synthesis. Am J Physiol 1999;277:E608–16.
[20] Zhang YA, Salinas I, Li J, Parra D, Bjork S, Xu Z, et al. IgT, a primitive immunoglobulin class specialized in mucosal immunity. Nat Immunol 2010;11:827–35.
[21] Puzianowska-Kuznicka M, Owczarz M, Wieczorowska-Tobis K, Nadowski P, Chudek J, Slusarczyk P, et al. Interleukin-6 and C-reactive protein, successful aging, and mortality: the PolSenior study. Immun Ageing 2016;13:21.
[22] Dutra MT, Avelar BP, Souza VC, Bottaro M, Oliveira RJ, Nobrega OT, et al. Relationship between sarcopenic obesity-related phenotypes and inflammatory markers in postmenopausal women. Clin Physiol Funct Imaging 2015;37(2):205–10.
[23] Atkins JL, Whincup PH, Morris RW, Wannamethee SG. Low muscle mass in older men: the role of lifestyle, diet and cardiovascular risk factors. J Nutr Health Aging 2014;18:26–33.
[24] Schaap LA, Pluijm SM, Deeg DJ, Visser M. Inflammatory markers and loss of muscle mass (sarcopenia) and strength. Am J Med 2006 Jun 30;l19(6):526–69.
[25] Fujikawa H, Araki T, Okita Y, Kondo S, Kawamura M, Hiro J, et al. Impact of sarcopenia on surgical site infection after restorative proctocolectomy for ulcerative colitis. Surg Today 2017;47:92–8.
[26] Roubenoff R. Sarcopenic obesity: the confluence of two epidemics. Obes Res 2004;12:887–8.
[27] Levine ME, Crimmins EM. The impact of insulin resistance and inflammation on the association between sarcopenic obesity and physical functioning. Obesity (Silver Spring) 2012;20:2101–6.
[28] Joppa P, Tkacova R, Franssen FM, Hanson C, Rennard SI, Silverman EK, et al. Sarcopenic obesity, functional outcomes, and systemic inflammation in patients with chronic obstructive pulmonary disease. J Am Med Dir Assoc 2016;17:712–8.
[29] Yang CW, Li CI, Li TC, Liu CS, Lin CH, Lin WY, et al. Association of sarcopenic obesity with higher Serum high-sensitivity C-Reactive protein levels in Chinese older males—a community-based study (Taichung Community Health Study-Elderly, TCHS-E). PLoS One 2015;10:e0132908.
[30] van de Bool C, Rutten EP, Franssen FM, Wouters EF, Schols AM. Antagonistic implications of sarcopenia and abdominal obesity on physical performance in COPD. Eur Respir J 2015 Apr 16. ERJ-01973.
[31] Plaisance EP, Grandjean PW. Physical activity and high-sensitivity C-reactive protein. Sports Med 2006;36:443–58.

[32] Church TS, Earnest CP, Thompson AM, Priest EL, Rodarte RQ, Saunders T, et al. Exercise without weight loss does not reduce C-reactive protein: the INFLAME study. Med Sci Sports Exerc 2010;42:708–16.

[33] Schaper F, Rose-John S. Interleukin-6: biology, signaling and strategies of blockade. Cytokine Growth Factor Rev 2015;26:475–87.

[34] Heinrich PC, Castell JV, Andus T. Interleukin-6 and the acute phase response. Biochem J 1990;265:621–36.

[35] Muraguchi A, Hirano T, Tang B, Matsuda T, Horii Y, Nakajima K, et al. The essential role of B cell stimulatory factor 2 (BSF-2/IL-6) for the terminal differentiation of B cells. J Exp Med 1998;187:332–44.

[36] Ambrosino DM, Delaney NR, Shamberger RC. Human polysaccharide-specific B cells are responsive to pokeweed mitogen and IL-6. J Immunol 1990;144:1221–6.

[37] Kania DM, Binkley N, Checovich M, Havighurst T, Schilling M, Ershler WB. Elevated plasma levels of interleukin-6 in postmenopausal women do not correlate with bone density. Am J Geriatr Soc 1995;43:236–9.

[38] Daynes RA, Araneo BA, Ershler WB, Maloney C, Li GZ, Ruy SY. Altered regulation of IL-6 production with normal aging. Possible linkage to the age-associated decline in dehydroepiandrosterone and its sulfated derivative. J Immunol 1993;150:5219–30.

[39] Foster KD, Conn CA, Kluger MJ. Fever, tumor necrosis factor, and interleukin-6 in young, mature, and aged Fischer 344 rats. Am J Physiol 1992;262:R211–5.

[40] Ershler WB, Keller ET. Age-associated increased interleukin-6 gene expression, late-life diseases, and frailty. Annu Rev Med 2000;51:245–70.

[41] Kim JK, Choi SR, Choi MJ, Kim SG, Lee YK, Noh JW, et al. Altered regulation of IL-6 production with normal aging. Possible linkage to the age-associated decline in dehydroepiandrosterone and its sulfated derivative. J Immunol 1993;150:5219–30.

[42] Phillips CM, Perry IJ. Does inflammation determine metabolic health status in obese and nonobese adults? J Clin Endocrinol Metab 2013;98:E1610–9.

[43] Na YK, Hong HS, Lee WK, Kim YH, Kim DS. Increased methylated of interleukin 6 gene is associated with obesity in Korean women. Mol Cells 2015;38:452–6.

[44] Cullen T, Thomas AW, Webb R, Hughes MG. Interleukin-6 and associated cytokine responses to an acute bout of high-intensity interval exercise: the effect of exercise intensity and volume. Appl Physiol Nutr Metab 2016;41:803–8.

[45] Wang CH, Chung MH, Chan P, Tsai JC, Chen FC. Effects of endurance exercise training on risk components for metabolic syndrome, interleukin-6, and the exercise capacity of postmenopausal women. Geriatr Nurs 2014;35:212–8.

[46] de Gonzalo-Calvo D, Nitzert K, Fernandez M, Vega-Naredo I, Caballero B, Garcia-Macia M, et al. Differential inflammatory responses in aging and disease: TNF-alpha and IL-6 as possible biomarkers. Free Radic Biol Med 2010;49:733–7.

[47] Luo G, Hershko DD, Robb BW, Wray CJ, Hasselgren PO. IL-1beta stimulates IL-6 production in cultured skeletal muscle cells through activation of MAP kinase signaling pathway and NF-kappa B. Am J Physiol Regul Integr Comp Physiol 2003;284:R1249–54.

[48] Dugdale HF, Owens DJ, Hughes DC, Stewart CE, Sharples AP. I-glutamine improves skeletal muscle cell differentiation and prevents myotube atrophy after cytokine (TNF-alpha) Stress via reduced p38 MAPK signal transduction. J Cell Physiol 2016;231:2720–32.

[49] Dinarello CA. Interleukin-1 in the pathogenesis and treatment of inflammatory diseases. Blood 2011;117:3720–32.

[50] Reid MB, Li YP. Tumor necrosis factor-alpha and muscle wasting: a cellular perspective. Respir Res 2011;12:269–72.

[51] Lang CH, Frost RA. Role of growth hormone, insulin-like growth factor-I, and insulin-like growth factor binding proteins in the catabolic response to injury and infection. Curr Opin Clin Nutr Metab Care 2002;5:271–9.

[52] Wang DT, Yin Y, Yang YJ, Lv PJ, Shi Y, Lu L, et al. Resveratrol prevents TNF-alpha-induced muscle atrophy via regulation of Akt/mTOR/Foxo1 signaling in C2C12 myotubes. Int Immunopharmacol 2014;19:206–13.

[53] Pistilli EE, Jackson JR, Alway SE. Death receptor-associated pro-apoptotic signaling in aged skeletal muscle. Apoptosis 2006;11:2115–26.

[54] Langen RC, Van Der Velden JL, Schols AM, Kelders MC, Wouters EF, Janssen-Heininger YM. Tumor necrosis factor-alpha inhibits myogenic differentiation through MyoD protein destabilization. FASEB J 2004;18:227–37.

[55] Shaap LA, Pluim SM, Deeg DJ, Harris TB, Kritchevsky SB, Newman AB, et al. Higher inflammatory marker levels in older persons: associations with 5-year change in muscle mass and muscle strength. J Gerontol A Biol Sci Med Sci 2009;64:1183–9.

[56] Greiwe JS, Cheng B, Rubin DC, Yarasheski KE, Semenkovich CF. Resistance exercise decreases skeletal muscle tumor necrosis factor alpha in frail elderly humans. FASEB J 2001;15:475–82.

[57] Zamir O, Hasselgren PO, Kunkel SL, Frederick J, Higashiguchi T, Fischer JE. Evidence that tumor necrosis factor-alpha participates in the regulation of muscle proteolysis during sepsis. Arch Surg 1992;127:170–4.

[58] El Maghraouil A, Ebbo O, Fadri S, Majjad A, Hamza T, Mounach A. Is there a relation between pre-sarcopenia, sarcopenia, cachexia and osteoporosis in patients with ankylosing spondylitis? BMC Musculoskelet Disord 2016;17:268.

[59] Coletti D, Moreisi V, Adamo S, Mollinaro M, Sassoon D. Tumor necrosis factor-alpha gene transfer induces cachexia and inhibits muscle regeneration. Genesis 2005;43:120–8.

[60] Nedwin GE, Naylor SL, Sakaguchi AY, Smith D, Jarrett-Nedwin J, Pennica D, et al. Human lymphotixin and tumor necrosis factor genes: structure, homology and chromosomal localization. Nucleic Acids Res 1985;13:6361–73.

[61] Wilson AG, Symons JA, McDowell TL, McDevitt HO, Duff GW. Effects of a polymorphism in the human tumor necrosis factor alpha promoter on transcriptional activation. Proc Natl Acad Sci U S A 1997;94:3195–9.

[62] Di Renzo L, Sarlo F, Petramala L, Iacopino L, Monteleone G, Florini JR, Ewton DZ, Coolican SA. Growth hormone and the insulin-like growth factor system in myogenesis. Endocr Rev 2003;24:989–1015.

[63] Higashiguchi T, Fischer JE. Evidence that tumor necrosis factor-alpha participates in the regulation of muscle proteolysis during sepsis. Cytokine Growth Factor Rev 1999;10:5–13.

[64] Schager MA, Metter EJ, Simonsick E, Ble A, Bandinelli S, Lauretani F, et al. Sarcopenic obesity and inflammation in the InCHIANTI study. J Appl Physiol 2007;102:919–25.

[65] Starkie R, Ostrowski SR, Jaafred F, Febbraio M, Pedersen BK. Exercise and IL-6 infusion inhibit endotoxin-induced TNF-alpha production in humans. FASEB J 2003;17:884–6.

[66] Florini JR, Ewton DZ, Coolican SA. Growth hormone and the insulin-like growth factor system in myogenesis. Endocr Rev 1996;17:481–517.

[67] Heemskerk VH, Daemen EA, Buurman WA. Insulin-like growth factor-1 (IGF-1) and growth hormone (GH) in immunity and inflammation. Cytokine Growth Factor Rev 1999;10:5–14.

[68] Aricochea T, Iriarte-Arguedas J, Cuesta S, Gratas Delamarque A, Tresguerres JA, Gomez-Cabreraz MC, et al. Growth hormone replacement therapy prevents sarcopenia by a dual mechanism: improvement of protein balance and of antioxidant defenses. J Gerontol A Biol Sci Med Sci 2014;69:1186–98.
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[69] Waters DL, Qualls CR, Dorin RI, Veldhuis JD, Baumgartner RN. Altered growth hormone, cortisol, and leptin secretion in healthy elderly persons with sarcopenia and mixed body composition phenotypes. J Gerontol A Biol Sci Med Sci 2008; 63:S36–41.

[70] Van Dam PS, Smid HE, de Vries WR, Niesink M, Bolscher E, Waasdorp EJ, et al. Reduction of free fatty acids by acipimox enhances the growth hormone (GH) responses to GH-releasing peptide 2 in elderly men. J Clin Endocrinol Metab 2000;85: 4706–11.

[71] Thomas GA, Kraemer WJ, Comstock BA, Dunn-Lewis C, Van Dam PS, Smid HE, de Vries WR, Niesink M, Bolscher E, Waters DL, Qualls CR, Dorin RI, Veldhuis JD, Baumgartner RN. Inflammation and Sarcopenia 101

[72] Dagdeviren S, Jung DY, Lee E, Friedline RH, Noh HL, Kim JH, Li Y, Li F, Lin B, Kong X, Tang Y, Yin Y. Myokine IL-15 regulates the metabolic syndrome in obese women. J Clin Endocrinol Metab 2003;88:1055.

[73] Emanuelli B, Peraldi P, Filloux C, Chavey C, Freidinger K, Bastard C, Witters L, Myers T, et al. Regulation of cellular hypertrophy by PI(3)K/Akt/mTOR and PI(3)K/Akt/GSK3 pathway in skeletal muscle. J Biol Chem 2001;276:124–32.

[74] Forsey RJ, Thompson JM, Ernerudh J, Hurst TL, Strindhall J, Alvarez-Rodriguez L, Lopez-Hoyos M, Munoz-Cacho P, Martino G, et al. Plasma cytokine profiles in elderly humans. Mech Ageing Dev 2003;124:487–93.

[75] Pedersen BK. The diseases of physical inactivity — and the role of cytokines in muscle — fat cross-talk. J Physiol 2009;587:5559–68.

[76] Ko F, Abadir P, Marx R, Westbrook R, Cooke C, Yang H, et al. Impaired mitochondrial degradation by autophagy in the skeletal muscle of the aged female interleukin 10 null mouse. Exp Gerontol 2016;73:23–7.

[77] Esposito K, Pontillo A, Giugliano F, Giugliano G, Marfella R, Nicoletti G, et al. Association of low interleukin-10 levels with obesity, growth hormone and exercise. Sports Med 2013;43:839–49.

[78] Alvarez-Rodriguez L, Lopez-Hoyos M, Munoz-Cacho P, Martinez-Taboada VM. Aging is associated with circulating cytokine dysregulation. Cell Immunol 2012;273:124–32.

[79] Forsey RJ, Thompson JM, Ernerudh J, Hurst TL, Strindhall J, Johansson B, et al. Plasma cytokine profiles in elderly humans. Mech Ageing Dev 2003;124:487–93.

[80] Pedersen BK. The diseases of physical inactivity — and the role of cytokines in muscle — fat cross-talk. J Physiol 2009;587:5559–68.

[81] Ko F, Abadir P, Marx R, Westbrook R, Cooke C, Yang H, et al. Impaired mitochondrial degradation by autophagy in the skeletal muscle of the aged female interleukin 10 null mouse. Exp Gerontol 2016;73:23–7.

[82] Esposito K, Pontillo A, Giugliano F, Giugliano G, Marfella R, Nicoletti G, et al. Association of low interleukin-10 levels with obesity, growth hormone and exercise. Sports Med 2013;43:839–49.