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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 circulatory 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].

Ageing has adverse effects on skeletal muscles. Sarcopaenia 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 sarcopaenia pathogenesis includes physical inactivity, malnutrition and increased oxidative stress [8]. Sarcopaenia in the elderly has become a significant public health problem. It is reportedly associated with osteoporosis, and people with sarcopaenia have higher fall risks than non-sarcopenic individuals [9,10]. Histologically, sarcopaenia 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 sarcopaenia. 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 sarcopaenia according to the existing research [3—5]. However, there is no clearly defined relationship between inflammation and sarcopaenia.

Therefore, this review aims to focus on the role of inflammatory cytokines and their corresponding molecular pathways that impact muscle metabolism in sarcopaenia. We further describe the involvement of chronic inflammation in sarcopaenia 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 sarcopaenia 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 sarcopaenia were included in this review. Thirteen additional studies that investigated signalling pathways involving the aforementioned cytokines related to sarcopaenia were selected from the originally retrieved 1036 papers. Papers not written in English (approximately 4.2%) were excluded.

Pathogenesis of Sarcopaenia

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 sarcopaenia [19].

C-Reactive Protein and Sarcopaenia

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 sarcopaenia showed significantly higher CRP concentrations as compared to those without sarcopaenia [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 sarcopaenia 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 sarcopaenia [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 sarcopaenia, remains uncertain. Van de Bool et al. investigated sarcopaenia 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 sarcopaenia, where circulatory CRP levels positively correlate with sarcopaenia 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 sarcopaenia by the European Working Group on Sarcopaenia in Older People.

Interleukin-6 and Sarcopaenia

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 sarcopaenia 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 ($r_s = 0.19$), fat mass ($r_s = 0.19$) and waist circumference ($r_s = 0.17$). 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 sarcopaenia, 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 sarcopaenia. 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 $\geq$ 30 kg/m^2) presented with significantly increased hypermethylation of the IL-6 gene compared to individuals with normal weight (BMI < 23 kg/m^2) and those who were overweight (BMI = 23–30 kg/m^2) ($p = 0.034$ 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 sarcopaenia.

Tumour Necrosis Factor-α and Sarcopaenia

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 super family), 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 sarcopaenia. 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 sarcopaenia, and TNF-α can also be a potential serum marker in individuals with sarcopaenia.

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 sarcopaenia [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 up-regulated 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 ($M^{IL\text{-}10}$) 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 (phosphatidylinositide 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.

Table 1 Summary of inflammatory cytokines related to sarcopaenia.

Inflammatory cytokines	Source	Function	Tendency in sarcopaenia	Related pathways
CRP	Liver	A marker of systemic inflammation	↑	
IL-6	T cells, macrophages, fibroblasts and endothelial cells	A pro-inflammatory cytokine and an anti-inflammatory myokine	↑	STAT3; MEK1; p38 MAPK; AMPK; PI3K
TNF-α	Macrophages	A pro-inflammatory cytokine	↑	NF-κB; JAK/STAT5
GH	Somatotroph in anterior pituitary gland	GH-IGF axis regulates the growth and differentiation of skeletal muscles	↓	Akt/mTOR; Akt/GSK
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 = interlukin; mTOR, mammalian target of rapamycin; TNF-α = tumour necrosis factor-α.

Moreover, as sarcopaenia 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 sarcopaenia. 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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