Int J Physiol Pathophysiol Pharmacol 2025;17(3):80-93
www.ijppp.org /ISSN:1944-8171/IJPPP0163699

Review Article

State-of-the-art insights into myokines as biomarkers of sarcopenia: a literature review

Omar R Moussaoui[1*], Ioannis Deligiannis[1*], Petar-Preslav Petrov[2], Tsvetelina Velikova[3], Yavor Assyov[4]

[1]Faculty of Medicine, Sofia Medical University, Sofia, Boulevard Akademik Ivan Evstratiev Geshov 15, 1431 Sofia, Bulgaria; [2]Department of Anatomy, Histology, and Embryology, Medical University of Plovdiv, Vasil Aprilov 15A, 4000 Plovdiv, Bulgaria; [3]Medical Faculty, Sofia University St. Kliment Ohridski, 1 Kozyak str, 1407 Sofia, Bulgaria; [4]Endocrinology Clinic, Aleksandrovska University Hospital, ul. "Sveti Georgi Sofiyski" 1, 1431 Sofia, Bulgaria. [*]Equal contributors.

Received February 4, 2025; Accepted June 8, 2025; Epub June 15, 2025; Published June 30, 2025

Abstract: Sarcopenia is an age-associated progressive deterioration of skeletal muscle, not only affecting the muscle function of elderly individuals but also contributing to various health issues and increased mortality. Current diagnostic tools are faced with limitations, hindering their widespread clinical application. This review examines the potential of myokines, peptides released from contracting muscles, as innovative biomarkers for sarcopenia. We explore the wide range of auto-, para-, and endocrine functions of myokines and the pathways of their physiological action, as well as address ongoing research results on the role of myokines as biomarkers for the timely diagnosis of sarcopenic individuals. Of all myokines, the ones that show the highest potential include irisin, myostatin, follistatin and brain-derived neurotrophic factor (BDNF). Their physiological action is exerted through complex pathways involving multiple molecules. Most studies show that these molecules can be used as biomarkers for the timely diagnosis of sarcopenia, whether by using each one individually or as a panel of biomarkers. However, several studies showed no correlation between the plasma levels of these peptides and a sarcopenia diagnosis. Finally, a number of studies also exhibited gender-affected relationships. While the quality of studies is promising, research on the use of myokines as biomarkers of sarcopenia is needed to more accurately determine the cut-off plasma values of such markers. By overcoming the shortcomings of existing methodologies, utilizing myokines in daily clinical practice could offer a promising path toward more effective prevention, diagnosis, and treatment strategies, ultimately improving outcomes for the aging population.

Keywords: Sarcopenia, myokine(s), biomarker, myostatin, irisin, follistatin, brain-derived neurotrophic factor

Introduction

Age-related disorders are growing increasingly common nowadays due to the unprecedented growth in both the size and proportion of the elderly population [1]. Sarcopenia, defined by progressive deterioration of skeletal muscle associated with age, carries high prevalence rates among these aging individuals and leads to various concomitant conditions, as well as increased mortality, which highlights the pressing need for more thorough understanding of the disease [2].

However, the diagnostic methods available nowadays, including dual-energy X-ray absorptiometry (DEXA) and computed tomography (CT), may have inaccuracies while requiring trained staff and high costs, thus proving unsuitable for large-scale use in everyday practice [3]. Another option is bioelectrical impedance analysis (BIA), which is also unsatisfactory due to relatively poor reproducibility [4].

Myokines are peptides or proteins secreted or released from skeletal muscle cells that exert auto-, para-, or endocrine functions [5]. Normal muscle function and mass maintenance depend on the dynamic balance between positive and negative regulators-myokines. Therefore, it may be possible to use these molecules as biomarkers for aging muscle atrophy and dysfunction and thus prove useful for diagnosing, preventing, and treating sarcopenia.

https://doi.org/10.62347/RNEQ8696

This review mainly focuses on the potential of four myokines to be used as potential biomarkers for diagnosing sarcopenia: myostatin, irisin, follistatin, and brain-derived neurotrophic factor (BDNF). By examining their physiological roles, mechanisms of action, and associations with muscle mass and function, we aim to highlight their potential diagnostic value and clinical relevance. We include the most recent and relevant evidence supporting their utility as biomarkers, their correlation with sarcopenia-related outcomes, and the potential challenges associated with their use in clinical practice. Additionally, the review explores how these myokines may vary across different populations, considering factors such as age, sex, and underlying health conditions, which could influence their reliability as diagnostic tools.

Search strategy

A comprehensive literature search from November 2024 to January 2025 was conducted across PubMed, Scopus, Web of Science, and MEDLINE to identify studies exploring myokines as biomarkers for sarcopenia. Both Medical Subject Headings (MeSH) and free-text terms were used to ensure comprehensive coverage. The search strategy combined keywords related to sarcopenia and biomarkers using Boolean operators: ("sarcopenia" OR "age-related muscle loss") AND ("myokines" OR "muscle-derived cytokines" OR "inflammatory biomarkers") AND ("diagnosis" OR "prognosis" OR "biomarker validation"). The Boolean search was further refined to include specific myokines of interest: ("myostatin" OR "irisin" OR "follistatin" OR "brain-derived neurotrophic factor") AND ("sarcopenia" OR "age-related muscle loss"), ensuring the inclusion of studies investigating these key biomarkers in the context of sarcopenia.

Articles were filtered by publication in English, relevance to the topic, and studies conducted in humans. The exclusion criteria were: papers written in non-English, published before 2005, animal studies, non-peer-reviewed materials, and papers not directly addressing sarcopenia. References from retrieved articles were also screened manually to identify additional relevant publications. The final selection of studies was based on their alignment with the research focus and the inclusion of data pertinent to the role of myokines in the diagnosis or prognosis of sarcopenia.

Definition and diagnosis of sarcopenia

In 2019, the global elderly population was estimated to be around 703 million people, and projections indicate an increase to 1.5 billion by 2050 [6]. According to a meta-analysis on the epidemiology of sarcopenia, it was stated that the pooled prevalence of all definitions was around 10% (95% CI 7%-12%) in Nascimento PR et al.'s study and 16% (95% CI 15%-17%) in Petermann-Rocha F et al.'s study [7]. This discrepancy could stem from differences in diagnostic criteria, methodologies, or population demographics. It is estimated that sarcopenia affected over 50 million individuals in this age bracket a decade ago, and the projection indicates that it will impact four times as many people in the next three decades. Sarcopenia is now officially recognized as a disease with an ICD-10-MC, thus highlighting its clinical importance. It is defined as a progressive and generalized skeletal muscle disorder that is associated with an increased likelihood of adverse outcomes like falls, fractures, physical disability, and increased mortality. It can be categorized as 'primary' (age-related) when no other specific cause is apparent, while it is termed secondary when causal factors other than or in addition to aging are present. It can develop because of a systemic disease, particularly one that may trigger inflammatory processes. Physical inactivity also plays a role in the onset of sarcopenia, whether caused by a sedentary lifestyle or immobility related to an illness [8]. Proinflammatory mediators discharged during systemic illnesses and the build-up of fat due to a sedentary way of life create a harmful loop, diminishing muscle strength, promoting physical inactivity, and exacerbating sarcopenia [9].

According to the 2018 definition by the European Working Group on Sarcopenic Obesity in Older People (EWGSOP2), low muscle strength is now considered the primary parameter for diagnosing sarcopenia, making it the most dependable measure of muscle function. Specifically, sarcopenia is likely when low muscle strength is identified, and a diagnosis is confirmed if there's also evidence of low muscle quality or quantity. If all three factors - low muscle strength, low muscle quality/quantity, and reduced physical performance - are present, then the condition of sarcopenia is classified as severe [8, 9]. The EWGSOP2's emphasis on low muscle strength shows that functional-

ity rather than structural integrity (muscle mass) plays a highly significant role in the development of the disorder. Measuring muscle strength, however, especially in frail or immobile individuals, can prove difficult, showcasing the need for more advanced diagnostic tools.

Since sarcopenia is a complex geriatric syndrome driven by multiple interrelated etiological factors, which include age-related hormonal decline (e.g., reduced levels of testosterone, estrogen, and growth hormone), chronic low-grade inflammation, sedentary lifestyle, and inadequate nutritional intake - particularly deficiencies in protein and vitamin D. These factors collectively impair muscle protein synthesis and promote catabolism, contributing to the progressive loss of muscle mass and function [10].

Sarcopenia can be divided into two distinct categories depending on its cause. Primary (age-related) sarcopenia occurs due to muscle deterioration associated with aging, without any other underlying cause, while secondary sarcopenia arises from additional contributing factors. The combination of prolonged inactivity and anabolic resistance, which results in fat accumulation and the release of proinflammatory cytokines, leads to muscle atrophy and reduced muscle strength. Risk factors for sarcopenia include age, sex, mitochondrial dysfunction, and decreased muscle regenerative capacity due to impaired satellite cell activity [10]. Certain medications, such as proton pump inhibitors (PPIs) and corticosteroids, can accelerate the progression of muscle loss in sarcopenia [11].

Currently, there is no approved pharmacological therapy for sarcopenia [12]. However, current treatment strategies are multifaceted, with resistance training recognized as the most effective non-pharmacologic intervention for improving muscle strength and performance. Nutritional supplementation, including increased dietary protein and vitamin D, is also essential to support muscle metabolism. In addition, pharmacological agents such as testosterone and selective androgen receptor modulators (SARMs) have shown promise in clinical studies. However, their routine use remains limited due to safety considerations and the need for further evidence [12].

The most important therapeutic strategies include resistance training and proper nutrition, particularly following a Mediterranean diet, to support muscle regeneration and maintenance. Nutritional targets include adequate protein intake and supplementation with micronutrients (vitamin D, magnesium, iron) and creatine, which may aid in muscle hydration [10, 11]. According to European guidelines, the recommended daily water intake is 1.6 liters for older women and 2 liters for older men [13]. Additionally, pharmacological options such as myostatin inhibitors (e.g., bimagrumab) [14] and anti-inflammatory therapies [15] are currently in clinical trials, but require further research. Lastly, anti-diabetic drugs may also help maintain muscle metabolism [12].

Moreover, physical exercise, particularly endurance training, can prove a powerful tool in managing sarcopenia. Muscle contraction during exercise produces myokines that promote the maintenance of skeletal muscle metabolism. Studies show that aerobic and anaerobic training can upregulate the expression of favorable myokines, like irisin, raising their blood levels and stimulating muscle regeneration. Additionally, this training can reduce myostatin levels, further counteracting muscle loss. Developing exercise programs incorporating both types of training is a promising direction and should be a topic of further research [16].

Myokines at a glance

Myokines, defined as cytokines or peptides synthesized, expressed, and released by skeletal muscle cells, with autocrine, paracrine or endocrine effects, represent an exciting frontier in the understanding of skeletal muscle's systemic role. While both the expression and release of myokines can be regulated by muscle contraction, this is not a mandatory property of all myokines [17]. This nuance invites further exploration of the mechanisms controlling myokine release under different states. The presence of myokines secreted during skeletal muscle contraction and their role in influencing metabolic and physiological responses in other organs, independent of the nervous system, was further demonstrated through experiments on paralyzed muscles, clearly showcasing the endocrine role of skeletal muscle. Specifically, electrical stimulation of paralyzed muscles in patients with spinal cord injuries lacking sen-

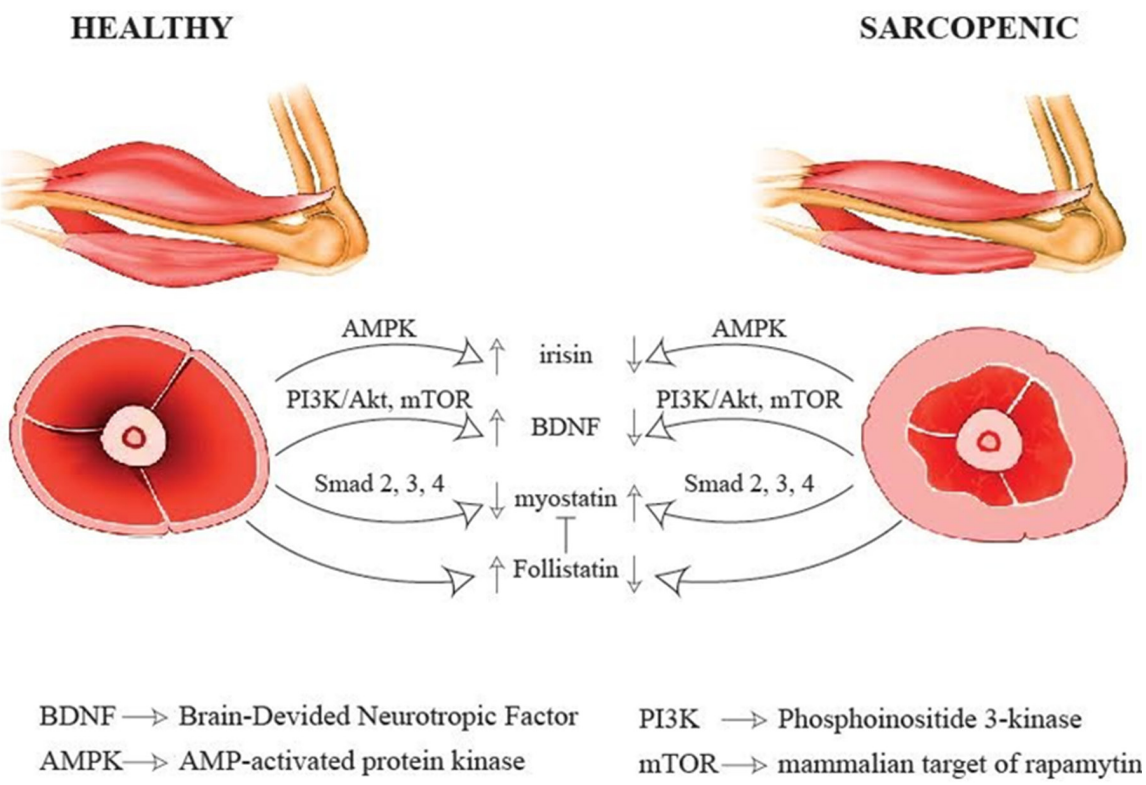

Figure 1. Myokine Levels in Healthy and Sarcopenic Individuals. Summary of the suggested level changes of myokines depending on the health status of the individual. The main physiological pathways by which these myokines are regulated are also included. This figure shows the suggested plasma level changes of the 4 researched myokines, depending on the health status of the individual. In general, healthy skeletal muscle shows increased levels of irisin and BDNF and reduced levels of myostatin (increased levels of follistatin are related to its inhibitory role). On the contrary, sarcopenic muscle is characterized by increased levels of myostatin and decreased levels of irisin and BDNF. The main physiological pathways by which myokines are regulated are also included. Irisin secretion is regulated by the AMPK pathway through the activation of PGC-1α, which promotes FNDC5 expression; BDNF secretion is regulated by the PI3K/Akt/mTOR pathway, which enhances its expression and release through transcriptional and translational mechanisms; Myostatin release is regulated by the SMAD2/3/4 pathway, which mediates its expression via TGF-β receptor signaling.

sory or motor impulses elicited similar physiological changes as observed in uninjured individuals [18].

With increasing age, myokines promoting muscle growth are down-regulated and worsen the proinflammatory, muscle-damaging environment associated with sarcopenia. This age-associated downregulation constitutes the main link between myokines and sarcopenia. This phenomenon likely contributes to the chronic proinflammatory state and loss of muscle function in older adults.

It is thus understood that myokines play a critical role in the regulation of muscle homeostasis and are closely linked to sarcopenia. The identification of reliable myokine biomarkers is crucial to better understand their role in the onset and progression of sarcopenia. Biomarkers would assist in the timely diagnosis of sarcopenic patients and assess the monitoring of the disease's progression and the efficacy of therapeutic interventions. It is important that sarcopenia biomarkers are aligned with the acceptable biomarker definition of "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention" [19]. While current evidence shows great promise, further research is essential to understand this complex relationship.

The suggested function of myokines is presented in **Figure 1**.

Myokines play a pivotal role in the diagnosis, prevention and treatment of sarcopenia. These myokines are being explored not only as diagnostic indicators but also as therapeutic targets. Inhibiting myostatin or enhancing beneficial myokines through exercise, pharmacological agents, or gene therapies offers promising avenues for preventing and treating sarcopenia. Thus, the modulation of myokine signaling represents an emerging and targeted strategy in managing age-related muscle decline.

These molecules are released from contracting muscle cells [20]. The blood levels of myokines can differ in healthy individuals and sarcopenic patients, thus denoting the presence of the disease. For instance, myostatin is often elevated in sarcopenic individuals, inhibiting muscle hypertrophy and promoting atrophy of muscle fibers [21]. Conversely, irisin enhances muscle regeneration through the Akt/mTOR signaling pathway and is crucial for normal muscle metabolism. Irisin levels are decreased in patients with sarcopenia and can serve as biomarkers for the early detection of the disease [22].

Irisin's function and its potential as a biomarker for sarcopenia

Irisin was first described in 2012 by Spiegelman [23]. As a cleaved form of fibronectin type III domain-containing protein 5 (FND5), it is controlled by PGC1-α (Peroxisome proliferator-activated receptor gamma coactivator 1-alpha). The reported positive correlation between serum irisin levels and muscle mass, strength, and metabolism in humans, alongside the negative correlation with fasting glycemia, underscores its potential in addressing sarcopenia. Irisin plays a role in controlling muscle development, mitochondrial activity, and metabolic balance within skeletal muscle. It enhances the production of PGC-1α, uncoupling protein 1 (UCP1), and other genes associated with brown (BAT) and white adipose tissue (WAT) to encourage "browning" and boost energy consumption [24]. Irisin levels in both men and women negatively correlate with advancing age. Furthermore, research by Chang et al. compared two distinct groups revealed lower irisin levels in the sarcopenia group compared to the normal group [25].

A meta-analysis of 32 studies, including 23,840 participants, and a comparison of 30 biomarkers for sarcopenia showed that irisin exhibited high levels of sensitivity and specificity as a potential biomarker. More specifically, three studies researching irisin included 967 participants and showed that the pooled specificity and sensitivity for all definitions were 67% (95% CI 59%-74%) and 78% (95% CI 72%-83%), respectively. In addition, the AUCs varied from 0.64 to 0.87, following the ROC curve analysis. However, the discriminatory power of a singular biomarker was deemed low-to-moderate, while the lack of standardized cut-off values posed an important limitation. According to the study, this could be solved with the construction of a diagnostic panel of multiple myokine-biomarkers that will be used for screening [26].

Qaisar et al. found that individuals at high risk for developing sarcopenia (defined as SARC-F score ≥4) had reduced levels of irisin compared to healthy controls [27]. They also observed a strong correlation between irisin levels and biceps circumference. The study also indicated that the levels of irisin are even lower in patients with sarcopenia, COPD, and CHF. This shows a clear association between irisin concentration and reduced muscle mass and strength in older individuals (all p-values <0.05), thus showing irisin's proposed role as a diagnostic marker. Additionally, there was an increase in irisin level in mice with increased musculature due to myostatin deficiency. Importantly, the research demonstrated that physical activity increases irisin levels and can play a protective role against muscle atrophy and lung impairment in individuals with COPD and secondary sarcopenia [27].

In another study showing the association between reduced irisin levels and sarcopenia, Alsaawi et al. demonstrated a strong connection between irisin levels and skeletal muscle mass (SMM) index as well as hand grip strength in elderly Arab women. Participants with elevated BMI were associated with a lower likelihood of having sarcopenia (odds ratio =0.79, P<0.001). Similarly, increased waist circumference and hip circumference also diminished the odds of sarcopenia (odds ratio =0.91, P<0.001) [28].

Yen et al. also discovered that irisin positively correlated with SMM and strength in a cross-

sectional study, including sarcopenic and non-sarcopenic individuals. According to their findings, the optimal cut-off value for predicting sarcopenia was 118.0 ng/ml, with a sensitivity of 0.8 and specificity of 0.5. Among the potential predictors of sarcopenia examined in this study (i.e., co-enzyme Q10, albumin, creatine kinase, irisin, and myostatin), irisin exhibited the highest area under the curve (AUC) value (0.64) and demonstrated consistent expression in statistical data compared to other predictors. Even after adjusting for confounding variables using logistic regression analyses, low levels of irisin remained significantly associated with an increased risk of sarcopenia (odds ratio =6.46, P<0.01) [4].

In a study by Baek et al., it was revealed that irisin levels decreased in sarcopenic patients compared to non-sarcopenic individuals (P= 0.001), contradicting earlier findings among South Koreans, which suggested no significant association between irisin and clinical muscle parameters [29]. This difference may stem from variations in sample size, assays utilized, and ethnic diversity concerning the current results. Moreover, the strong association between irisin and SMM index, as found in this research, aligns with earlier cross-sectional studies carried out among male and female individuals of Caucasian and African American descent over 35 years old. However, a different study of obese Chinese adults showed an opposite relationship, indicating that irisin levels were negatively linked to waist circumference [30].

Chang et al. demonstrated a negative association between circulating irisin levels and age in both men and women [25]. Additionally, they observed significantly lower mean circulating irisin levels in the elderly compared to young and middle-aged adults of both genders. The study also revealed that muscle mass and strength values were notably lower in older individuals, while waist-to-height ratio (WHTR) and body fat percentage were higher. Furthermore, when categorizing patients based on muscle condition, it was found that mean circulating irisin levels were lower in the pre-sarcopenia and sarcopenic groups than in the normal group for both sexes. In men, the ideal cut-off value for serum irisin concentrations was less than 1.00 μg/ml. For women, this threshold was below 1.16 μg/ml, with a sensitivity and specificity of 0.92 and 0.83, and 0.77 and 0.67, respectively. When predicting sarcopenia, unadjusted irisin levels showed an AUC of 0.873 in men and 0.685 in women across all models, with a *p*-value lower than <0.01 in each case. The sex-based differences in irisin levels and their association with sarcopenia add another layer of complexity. Discrepancies may be explained by differences in body composition between sexes as well as sex steroid hormones; however, further analysis considering confounding factors such as age could enhance diagnostic accuracy, particularly for women [25]. The AUCs for predicting sarcopenia with irisin, after adjusting for age, BMI and WHtR, were 0.942 in males and 0.804 in females, demonstrating enhanced discriminatory capability. Contrary to the findings of this research, a different study indicated that serum irisin levels showed no variation with muscle mass in an analysis involving both male and female subjects. However, the criteria used in that study to define sarcopenia differed from the guidelines proposed by the Asian Working Group for Sarcopenia (AWGS) [31].

Park et al. discovered that postmenopausal women with sarcopenia had notably lower levels of circulating irisin compared to healthy subjects. They also found that the association between irisin levels and the prevalence of sarcopenia remained significant even after accounting for other influencing factors. Additionally, their findings indicated that a decrease of 1 ng/ml in serum irisin concentration was associated with a 95% increase in the relative risk of developing sarcopenia [32]. A circulating level of 8.46 ng/ml was proposed as the threshold for irisin concentration, showing a sensitivity of 68% and specificity of 69%.

However, Choi et al. reported conflicting results, finding no variations in circulating irisin levels related to muscle mass. The divergent outcome could be attributed to the varying baseline characteristics of the study participants [33], emphasizing the need for standardized methodologies.

Lastly, a systematic review showed a positive relationship between serum irisin levels and SMI and HGS in cancer patients (P<0.001). The results of multiple linear regression analyses demonstrated that serum irisin independently

predicted sarcopenia in the study's population [34].

Previous studies have shown ethnic, regional, and comorbidity variations in the role of irisin as a biomarker for sarcopenia [27]. For instance, Alsaawi et al. reported strong correlations between irisin levels and muscle parameters in Arab women, while studies on South Korean and Chinese populations yielded conflicting findings. Reflecting genetic, environmental, or lifestyle factors that may influence irisin expression and function underscores the importance of cross-population studies [28].

Myostatin's potential as a biomarker for sarcopenia: age and sex variability

Myostatin is another myokine that could potentially play a role in the pathogenesis of sarcopenia. Also referred to as growth/differentiation factor 8, it is a member of the transforming growth factor β (TGF-β) family and is released from skeletal muscle cells [35]. Myostatin is involved in the suppression of genes related to skeletal muscle differentiation. Additionally, it activates protein degradation and hinders the positive regulation system of protein synthesis [36]. Finally, according to Mancinelli et al., myostatin is viewed as a myokine that promotes oxidative stress by generating reactive oxygen species in muscle cells through TNF-α signaling via NF-kB and NADPH oxidase [37]. The excessive expression of myostatin has been demonstrated to stimulate significant TNF-α production [38]. As individuals grow older, there is a potential for an increase in myostatin levels, which could contribute to the onset of age-related muscle loss and reduced strength. Research indicates that older adults with heightened myostatin levels had a significantly higher likelihood of displaying diminished handgrip strengths [39]. However, these conclusions vary in the literature, and some studies have not been able to establish a link between serum myostatin and aging or sarcopenia. Nevertheless, it is crucial to acknowledge the importance of myostatin and its impact on muscle atrophy, as it has been proven to significantly influence muscle growth signaling pathways and muscle mass.

Alexopoulos et al. explored myostatin's diagnostic utility and proposed that the ratios log-10myostatin-to-creatine phosphokinase (CPK) or albumin-to-myostatin demonstrate acceptable diagnostic accuracy for the prediction of sarcopenia in subjects with liver cirrhosis [40]. The study found that the optimal performance score in patients with a Model for End-Stage Liver Disease (MELD) was higher than 15. It was observed that myostatin levels were positively associated with skeletal muscle index in the patient group, even after adjusting for age, showing higher myostatin levels in non-severe sarcopenia compared to severe sarcopenia. While serum myostatin alone was not able to differentiate between sarcopenic and non-sarcopenic patients, the suggested ratios of log-10myostatin-to-CPK or albumin-to-myostatin proved more effective. In the case of ROC curve analyses, serum myostatin alone could not exclude sarcopenia. However, log10myostatin (pg/mL)-to-CPK (IU/L) and albumin-to-myostatin ratios demonstrated sufficient diagnostic precision in identifying sarcopenic patients, with AUCs 0.731 and 0.728, respectively. The cut-off value of 0.0448 for the log10myostatin-to-CPK ratio demonstrated a sensitivity of 0.85 and specificity of 0.5, while a cut-off value of 2.206×107 for the albumin-to-myostatin ratio showed a sensitivity of 0.85 plus specificity of 0.49. In cases where both markers fell below their respective cut-off values indicated above, 100% of the patients did not have sarcopenia and did not require further investigation using specialized tools [40]. Multiple researchers have found an inverse correlation between muscle mass and myostatin [41]. However, this inconsistency may be attributed to the fact that most of them relied on myostatin mRNA expression as a methodological approach.

In another study, Nishikawa et al. proposed a sarcopenia index based on GDF-15 (Growth/differentiation factor 15) and myostatin levels, which could indicate sarcopenia. The formula they suggested incorporates age, sex, BMI, as well as the concentrations of GDF-15 and myostatin and is as follows: {-0.0042 × [myostatin]} + {0.0007 × [GDF-15]} + (0.0890 × age) + (1.4030 × sex) - (0.0679 × BMI) - 2.1186. Plotting of a ROC curve showed that this index was a determinant of sarcopenia with a cut-off value of 1.0634, while the AUC was found to be 0.901, the sensitivity 96.9% and the specificity 70.9%. Their study found that SMI (Skeletal Muscle Index), HGS (Handgrip Strength), and

walking speed were inversely associated with GDF-15 concentration but positively associated with myostatin concentrations in patients undergoing cardiovascular surgery. Furthermore, patients with sarcopenia exhibited higher levels of GDF-15 and lower levels of myostatin, in contrast to previous findings [42]. In an interesting study, Czaja-Stolc et al. suggest a new formula that can be used to predict the likelihood of sarcopenia diagnosis in dialysis patients [43]. This formula incorporates age and the concentrations of albumin, adiponectin and myostatin and is as follows: log of odds ratio = 2.565 + (age × 0.0019) - {[albumin] × 0.0725} - {[adiponectin] × 0.0304} - {[myostatin] × 0.0005}. The AUC for this formula was 0.806, showing a positive predictive value of 61.54% and a negative predictive value of 79.78%.

Finally, in individuals following an ST-elevation myocardial infarction, serum myostatin levels were found to be associated with muscle mass and strength, with lower myostatin associated with an increased risk of in-hospital mortality [44].

In a cross-sectional study, Chew et al. demonstrated that mean normalized myostatin levels were significantly associated with sarcopenia in men (P=0.03), while serum IGF-1 levels correlated with impaired muscle function in women but not in men (P=0.046) [45]. These findings point to distinct, sex-specific pathways in the development of sarcopenia, suggesting that myostatin regulation of muscle mass plays a role in sarcopenia, primarily in men. The age-related decline in myostatin levels in men may reflect an adaptive response to unfavorable metabolic conditions [46] or changes in sex hormones [47]. Similarly, according to Tay et al., myostatin is a significant risk factor for sarcopenia, especially in men. However, this team found no significant difference in serum myostatin levels between sarcopenic and non-sarcopenic individuals (P=0.257) [39].

Lastly, in a cross-sectional study by Bergen et al., a novel mass spectrometry-based assay was used to demonstrate that circulating myostatin, a regulator of muscle mass in men, was most concentrated in young males and declined with age. In contrast, myostatin levels in women increased with age, suggesting its potential role as a mediator of sarcopenia in females [48]. This suggests that the measurement of myostatin serum levels should be adjusted for age and sex to predict sarcopenia accurately.

Follistatin: an uncertain biomarker for sarcopenia

Follistatin, a component of the TGFβ superfamily, serves as an inherent inhibitor of myostatin and is crucial in regulating skeletal muscle [49]. Research has indicated that follistatin levels in the bloodstream rise with physical activity, suggesting its significance in muscle function. Furthermore, it should be emphasized that the liver also produces this particular signaling molecule [9].

In a cross-sectional study involving postmenopausal women, Du et al. observed that subjects with sarcopenia had a higher likelihood of having elevated follistatin levels (P=0.01) [3]. The research involved 478 healthy postmenopausal women between 50 and 90 years. Sarcopenia was defined based on criteria set by WHO and AWGS. The findings indicated a correlation between elevated follistatin levels and decreased muscle strength and BMD, aligning with Fife et al.'s suggestion that myostatin and follistatin levels in circulation negatively affect muscle function in older women. In their study, healthy women exhibited follistatin (ng/ml) levels averaging 13.0 ± 4.9, whereas sarcopenic women demonstrated average levels of 18.97 ± 6.1 (P=0.027) [3, 48]. Despite the fact that follistatin is a potent inhibitor of myostatin-related muscle wasting, it showed a negative correlation with muscle mass [50].

Moreover, similar to previous research, Liaw et al. found a negative correlation between follistatin levels and gait speed in adults aged 65 or older. They observed that higher serum follistatin levels were associated with lower gait speed and elevated myostatin levels in the circulation. After accounting for age, sex and health behaviors, the β coefficient indicated a decrease of 0.308 in gait speed for each additional pg/ml of serum follistatin (P<0.001) [50].

On the other hand, Hofmann et al., in their study involving 98 women, found no disparities in follistatin levels between younger and elderly women. Their research revealed that the serum concentrations of follistatin were significantly almost identical among young, healthy and sarcopenic elderly women (P<0.05) [51]. Similar

findings were observed in other studies, including investigations into the levels of circulating activin A in elderly males [52].

According to Choi et al., there was a tendency for serum follistatin levels to show a negative correlation with the psoas muscle index (PMI) in men. Still, it did not reach statistical significance (P=0.055). However, this correlation was found to be significant in female patients (P= 0.034) [53]. Therefore, further research needs to be conducted regarding follistatin to achieve consensus on its status as a biomarker for sarcopenia.

Conversely, an analytical cross-sectional study performed by Aryana et al. showed no correlation between follistatin levels and sarcopenia in the elderly (P=0.615) [54]. The findings of this study align with those of a systematic review by Marguti et al., which concluded that follistatin, along with four other potential biomarkers, was not associated with sarcopenia [55].

Brain-derived neurotrophic factor's role as a biomarker for sarcopenia: a link between the nervous system and skeletal muscles

BDNF belongs to the neurotrophin family but can be seen as a myokine even in its roles in muscle repair, regeneration, and differentiation [56]. Most circulating BDNF originates from megakaryocytes, and physical exercise activates platelets to release BDNF into the circulation [57]. BDNF is broadly involved in several aspects of motor unit function, including regulating motor neuron survival during embryonic development and possibly during aging, enhancing presynaptic release of neurotransmitters and postsynaptic regulation of receptor expression [58]. This neuromuscular junction (NMJ) integration is a central focal point in the multifactorial etiology of sarcopenia. NMJ serves as a link between the nervous system (motor neurons) and skeletal muscle (myofibers) [59]. Aging contributes to NMJ dysfunction, muscle decline, and ultimately, the loss of muscle strength and mass that characterize it, which are partially restored by BDNF release following rehabilitation [60].

According to research conducted by Koito et al. in kidney transplant recipients, the average serum BDNF levels were significantly lower in the group with low skeletal muscle index compared to the healthy group (P=0.013). ROC analysis determined that the optimal cut-off value for serum BDNF levels was 17.8 ng/ml (with sarcopenic patients showing an average of 15.7 ng/ml). The study also found a positive association between BDNF levels and metabolic equivalents (METs - equal to 3.5 ml of O2 per kg of body weight x min), which in this study were used to express physical activity intensity (P<0.01) [61].

In addition, Karim and colleagues demonstrated that patients with COPD who were otherwise healthy had significantly reduced levels of BDNF compared to healthy individuals (30.3% decrease, P<0.05). The levels of these biomarkers only partially recovered after pulmonary rehabilitation. Furthermore, COPD patients with lower SARC-F scores, indicating limited physical activity, also exhibited decreased BDNF levels. The potential of BDNF for diagnosing sarcopenia was evaluated using ROC curves, which revealed an AUC of 0.757 and P<0.001. When a biomarker panel consisting of BDNF, GDNF, and CAF-22 was employed, the AUC increased further to 0.811 (P<0.001) compared to individual biomarkers alone in the diagnosis of sarcopenia [62]. The research team conducted a similar investigation involving individuals with Parkinson's disease. Following ROC analysis, the AUC for predicting BDNF probability was 0.746 (P<0.001). Consistent with prior research, the AUC notably improved to 0.821 after employing a panel of three biomarkers in diagnosing sarcopenia (P<0.001) [63].

Separate research conducted by Miyazaki and colleagues found that Japanese maintenance hemodialysis patients with sarcopenia had notably lower plasma BDNF levels. Nonetheless, the odds ratio per 100 pg/mL of BDNF for severe sarcopenia prevalence was not statistically significant (odds ratio: 0.470, P=0.062) [57].

In their review, Wei et al. emphasize the complex interaction between sex hormones, genetic influences, and epigenetic mechanisms in regulating BDNF signaling [64]. Sex hormones (estrogen and testosterone) modulate BDNF signaling in distinct ways, with estrogen often enhancing BDNF expression and testosterone influencing it via direct and indirect pathways.

Table 1. Studies on the potential of irisin, myostatin, follistatin and BDNF as biomarkers for sarcopenia

Biomarker	Study/ Evidence	Study Population		Definition Criteria for Sarcopenia	Impact	Study Design
		Median Age	Participants			
Irisin	Rizwan et al.	55-74	258	EWGSOP	Negative	Cohort
Irisin	Chi-Hua et al.	74.8 ± 7.4 for sarcopenic subjects & 72.0 ± 8.4 for non-sarcopenic subjects	99	AWGS	Negative	Cross-Sectional
Irisin	Alsaawi et al.	65.9 ± 5.5	131	AWGS	Negative	Cross-Sectional
Irisin	Chang et al.	18-90	715	AWGS	Negative	Cross-Sectional
Irisin	Park et al.	72.2 ± 5.96	153	Qc CSA/BW, Hand grip strength, SPPB score	Negative	Cohort
Irisin	Choi et al.	61 for sarcopenic subjects & 52 for non-sarcopenic subjects	401	SMMI of 2 SD below the sex-specific mean value for a younger reference group, ASM/height2 of 2 SD below the sex-specific mean value for a younger reference group	Neutral	Cohort
Irisin	Demir et al.	61.46 for sarcopenic subjects & 59.84 for non-sarcopenic subjects	141	EWGSOP	Negative	Cross-Sectional
Myostatin	Czaja-Stolc et al.	56.1 ± 16.3	180	EWGSOP	Dependant	Cross-Sectional
Myostatin	Chew et al.	67.9 ± 7.9	200	AWGS	Dependant	Cross-Sectional
Myostatin	Tay et al.	69.9 ± 7.9	200	AWGS	No Impact	Cross-Sectional
Myostatin	Bergen et al.	N/A	240	N/A	Dependant	Cross-Sectional
Myostatin	Alexopoulos et al.	59 for males & females	115	EWGSOP	Dependant	Cohort
Myostatin	Yamada et al.	56 ± 14	69	Serum creatinine level, Total creatinine excretion and lean body mass (LBM)		
Myostatin	Nishikawa et al.	68.5 for males & 74 for females	120	BIA measurement, MTH measurement	Dependant	Cross-Sectional
Follistatin	Du et al.	58.0 ± 4.0 for women aged <65 years, 69.21 ± 2.9 for women aged 65-75 years & 79.8 ± 3.6 for women above 75 years	478	AWGS	Positive	Cross-Sectional
Follistatin	Aryana et al.	68.57	75	AWGS	No Impact	Cross-Sectional
Follistatin	Liaw et al.	75.51 ± 7.61	205	Grip strength, walking time, gait speed	Positive	Cross-Sectional
Follistatin	Hofmann et al.	81	98	EWGSOP	Neutral	Cross-Sectional
Follistatin	Choi et al.	59	238	PMI measured at the L3 level in CT	Dependant	Cross-Sectional
BDNF	Koita et al.	52.1 ± 11.7	40	AWGS	Negative	Cross-Sectional
BDNF	Håkansson et al.	70.8 ± 0.8	19	N/A	Increasing	Cross-Sectional
BDNF	Karim et al.	68.3 ± 6.4 for healthy individuals, 71.2 ± 6.5 for patients with PD at diagnosis & 71.8 ± 6.5 at follow-up	142	EWGSOP	Negative	Cohort
BDNF	Miyazaki et al.	76.5	20	AWGS	Negative	Cross-Sectional

Abbreviations: EWGSOP: European Working Group on Sarcopenia in Older People; AWGS: Asian Working Group for Sarcopenia; Qc CSA/BW: Quadriceps Cross-Sectional Area/Body Weight; SPPB score: Short Physical Performance Battery; SMMI: Skeletal Muscle Mass Index; ASM: Appendicular Skeletal Muscle; PMI: Psoas muscle index; MTH: Muscle thickness of thigh; BIA: Bioelectrical Impedance Analysis.

This emphasizes the need for more comprehensive studies involving both sexes to understand these mechanisms and establish sex-specific plasma cut-off values thoroughly.

Moreover, in a study involving 19 healthy adults, Håkansson et al. showed that serum BDNF levels increased upon acute physical exercise [65]. As a result, measurements for the determination of BDNF plasma levels should be performed at least 24 hours following the last acute physical exercise [49].

To sum up, the data so far classify BDNF as a multifaceted molecule playing a critical role in muscle repair and differentiation. Its role as a biomarker for sarcopenia remains a topic of ongoing research, which should clarify the influence of sex hormones, genetic variations and physical exercise on its levels.

We summarize the main studies we have included in our review (**Table 1**). This table demonstrates the biomarkers mentioned, study population characteristics (median age and number of participants), and type of study for each article used in our review. Moreover, it displays the criteria used to define sarcopenia by each author and the suggested impact that each biomarker has.

Conclusions

As the global population continues to age at a surprisingly high rate, diseases related to aging are projected to pose a major challenge for health systems globally. Research has demonstrated that abnormal expression and secretion of myokines from aging muscle cells play an important and direct role in the development of sarcopenia and its associated conditions. The growing understanding of the roles of myokines, such as irisin, myostatin, follistatin, and BDNF, in the development of sarcopenia, presents a promising opportunity for early detection and intervention. By using myokines as biomarkers for sarcopenia, healthcare professionals may be able to identify individuals at risk or in the initial stages of the condition, allowing for timely interventions to reduce its progression and giving them the opportunity for personalized treatments that enhance health span and quality of life for aging individuals.

Disclosure of conflict of interest

In compliance with the ICMJE uniform disclosure form, all authors declare the following: Payment/services info: All authors have declared that no financial support was received from any organization for the submitted work. Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. Other relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

Address correspondence to: Ioannis Deligiannis, Faculty of Medicine, Sofia Medical University, Sofia, Boulevard Akademik Ivan Evstratiev Geshov 15, 1431 Sofia, Bulgaria. Tel: +30-6970267049; E-mail: giandeligiannis10@gmail.com

References

[1] Jedrychowski MP, Wrann CD, Paulo JA, Gerber KK, Szpyt J, Robinson MM, Nair KS, Gygi SP and Spiegelman BM. Detection and quantitation of circulating human irisin by tandem mass spectrometry. Cell Metab 2015; 22: 734-740.

[2] Santilli V, Bernetti A, Mangone M and Paoloni M. Clinical definition of sarcopenia. Clin Cases Miner Bone Metab 2014; 11: 177-180.

[3] Du Y, Xu C, Shi H, Jiang X, Tang W, Wu X, Chen M, Li H, Zhang X and Cheng Q. Serum concentrations of oxytocin, DHEA and follistatin are associated with osteoporosis or sarcopenia in community-dwelling postmenopausal women. BMC Geriatr 2021; 21: 542.

[4] Yen CH, Chang PS, Chang YH and Lin PT. Identification of coenzyme Q10 and skeletal muscle protein biomarkers as potential factors to assist in the diagnosis of sarcopenia. Antioxidants (Basel) 2022; 11: 725.

[5] Eckel J. Skeletal muscle: a novel secretory organ. In: Eckel J, editors. The Cellular Secretome and Organ Crosstalk. Academic Press; 2018 pp. 65-90.

[6] DellaPergola S. World Jewish population, 2012. In: Dashefsky A, Sheskin I, editors. American Jewish Year Book 2012. Dordrecht: Springer; 2013; 109-112: 213-283.

[7] Yuan S and Larsson SC. Epidemiology of sarcopenia: prevalence, risk factors, and consequences. Metabolism 2023; 144: 155533.

[8] Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyère O, Cederholm T, Cooper C, Landi F, Rol-

land Y, Sayer AA, Schneider SM, Sieber CC, Topinkova E, Vandewoude M, Visser M and Zamboni M; Writing Group for the European Working Group on Sarcopenia in Older People 2 (EWGSOP2), and the Extended Group for EWGSOP2. Sarcopenia: revised European consensus on definition and diagnosis. Age Ageing 2019; 48: 601.

[9] Barbalho SM, Flato UAP, Tofano RJ, Goulart RA, Guiguer EL, Detregiachi CRP, Buchaim DV, Araújo AC, Buchaim RL, Reina FTR, Biteli P, Reina DOBR and Bechara MD. Physical exercise and myokines: relationships with sarcopenia and cardiovascular complications. Int J Mol Sci 2020; 21: 3607.

[10] Cacciatore S, Calvani R, Esposito I, Massaro C, Gava G, Picca A, Tosato M, Marzetti E and Landi F. Emerging targets and treatments for sarcopenia: a narrative review. Nutrients 2024; 16: 3271.

[11] Zheng Y, Feng J, Yu Y, Ling M and Wang X. Advances in sarcopenia: mechanisms, therapeutic targets, and intervention strategies. Arch Pharm Res 2024; 47: 301-324.

[12] Mellen RH, Girotto OS, Marques EB, Laurindo LF, Grippa PC, Mendes CG, Garcia LNH, Bechara MD, Barbalho SM, Sinatora RV, Haber JFDS, Flato UAP, Bueno PCDS, Detregiachi CRP and Quesada K. Insights into pathogenesis, nutritional and drug approach in sarcopenia: a systematic review. Biomedicines 2023; 11: 136.

[13] Volkert D, Beck AM, Cederholm T, Cruz-Jentoft A, Hooper L, Kiesswetter E, Maggio M, Raynaud-Simon A, Sieber C, Sobotka L, van Asselt D, Wirth R and Bischoff SC. ESPEN practical guideline: clinical nutrition and hydration in geriatrics. Clin Nutr 2022; 41: 958-989.

[14] Ryan AS and Li G. Skeletal muscle myostatin gene expression and sarcopenia in overweight and obese middle-aged and older adults. JCSM Clin Rep 2021; 6: 137-142.

[15] Landi F, Marzetti E, Liperoti R, Pahor M, Russo A, Martone AM, Colloca G, Capoluongo E and Bernabei R. Nonsteroidal anti-inflammatory drug (NSAID) use and sarcopenia in older people: results from the ilSIRENTE study. J Am Med Dir Assoc 2013; 14: 626.e9-626.e13.

[16] Kwon JH, Moon KM and Min KW. Exercise-induced myokines can explain the importance of physical activity in the elderly: an overview. Healthcare (Basel) 2020; 8: 378.

[17] Pedersen BK and Febbraio MA. Muscles, exercise and obesity: skeletal muscle as a secretory organ. Nat Rev Endocrinol 2012; 8: 457-465.

[18] Kjaer M, Secher NH, Bangsbo J, Perko G, Horn A, Mohr T and Galbo H. Hormonal and metabolic responses to electrically induced cycling during epidural anesthesia in humans. J Appl Physiol (1985) 1996; 80: 2156-2162.

[19] Biomarkers Definitions Working Group. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. Clin Pharmacol Ther 2001; 69: 89-95.

[20] Scisciola L, Fontanella RA, Surina, Cataldo V, Paolisso G and Barbieri M. Sarcopenia and cognitive function: role of myokines in muscle brain cross-talk. Life (Basel) 2021; 11: 173.

[21] Bilski J, Pierzchalski P, Szczepanik M, Bonior J and Zoladz JA. Multifactorial mechanism of sarcopenia and sarcopenic obesity. Role of physical exercise, microbiota and myokines. Cells 2022; 11: 160.

[22] Inyushkin AN, Poletaev VS, Inyushkina EM, Kalberdin IS and Inyushkin AA. Irisin/BDNF signaling in the muscle-brain axis and circadian system: a review. J Biomed Res 2023; 38: 1-16.

[23] Boström P, Wu J, Jedrychowski MP, Korde A, Ye L, Lo JC, Rasbach KA, Boström EA, Choi JH, Long JZ, Kajimura S, Zingaretti MC, Vind BF, Tu H, Cinti S, Højlund K, Gygi SP and Spiegelman BM. A PGC1-α-dependent myokine that drives brown-fat-like development of white fat and thermogenesis. Nature 2012; 481: 463-468.

[24] Dong J, Dong Y, Dong Y, Chen F, Mitch WE and Zhang L. Inhibition of myostatin in mice improves insulin sensitivity via irisin-mediated cross talk between muscle and adipose tissues. Int J Obes (Lond) 2016; 40: 434-442.

[25] Chang JS, Kim TH, Nguyen TT, Park KS, Kim N and Kong ID. Circulating irisin levels as a predictive biomarker for sarcopenia: a cross-sectional community-based study. Geriatr Gerontol Int 2017; 17: 2266-2273.

[26] Lian R, Liu Q, Jiang G, Zhang X, Tang H, Lu J and Yang M. Blood biomarkers for sarcopenia: a systematic review and meta-analysis of diagnostic test accuracy studies. Ageing Res Rev 2024; 93: 102148.

[27] Qaisar R, Karim A, Muhammad T, Shah I and Khan J. Prediction of sarcopenia using a battery of circulating biomarkers. Sci Rep 2021; 11: 8632.

[28] Alsaawi TA, Aldisi D, Abulmeaty MMA, Khattak MNK, Alnaami AM, Sabico S and Al-Daghri NM. Screening for sarcopenia among elderly Arab females: influence of body composition, lifestyle, irisin, and vitamin D. Nutrients 2022; 14: 1855.

[29] Baek JY, Jang IY, Jung HW, Park SJ, Lee JY, Choi E, Lee YS, Lee E and Kim BJ. Serum irisin level is independent of sarcopenia and related muscle parameters in older adults. Exp Gerontol 2022; 162: 111744.

[30] Huh JY, Mougios V, Kabasakalis A, Fatouros I, Siopi A, Douroudos II, Filippaios A, Panagiotou G, Park KH and Mantzoros CS. Exercise-induced irisin secretion is independent of age or fitness level and increased irisin may directly

modulate muscle metabolism through AMPK activation. J Clin Endocrinol Metab 2014; 99: E2154-E2161.
[31] Choi HY, Kim S, Park JW, Lee NS, Hwang SY, Huh JY, Hong HC, Yoo HJ, Baik SH, Youn BS, Mantzoros CS and Choi KM. Implication of circulating irisin levels with brown adipose tissue and sarcopenia in humans. J Clin Endocrinol Metab 2014; 99: 2778-2785.
[32] Park HS, Kim HC, Zhang D, Yeom H and Lim SK. The novel myokine irisin: clinical implications and potential role as a biomarker for sarcopenia in postmenopausal women. Endocrine 2019; 64: 341-348.
[33] Choi K, Jang HY, Ahn JM, Hwang SH, Chung JW, Choi YS, Kim JW, Jang ES, Choi GH and Jeong SH. The association of the serum levels of myostatin, follistatin, and interleukin-6 with sarcopenia, and their impacts on survival in patients with hepatocellular carcinoma. Clin Mol Hepatol 2020; 26: 492-505.
[34] Demir L and Oflazoğlu U. The relationship between sarcopenia and serum irisin and TNF-α levels in newly diagnosed cancer patients. Support Care Cancer 2023; 31: 586.
[35] Consitt LA and Clark BC. The vicious cycle of myostatin signaling in sarcopenic obesity: myostatin role in skeletal muscle growth, insulin signaling and implications for clinical trials. J Frailty Aging 2018; 7: 21-27.
[36] White TA and LeBrasseur NK. Myostatin and sarcopenia: opportunities and challenges - a mini-review. Gerontology 2014; 60: 289-293.
[37] Mancinelli R, Checcaglini F, Coscia F, Gigliotti P, Fulle S and Fanò-Illic G. Biological aspects of selected myokines in skeletal muscle: focus on aging. Int J Mol Sci 2021; 22: 8520.
[38] Alizadeh Pahlavani H. Exercise therapy for people with sarcopenic obesity: myokines and adipokines as effective actors. Front Endocrinol (Lausanne) 2022; 13: 811751.
[39] Tay L, Ding YY, Leung BP, Ismail NH, Yeo A, Yew S, Tay KS, Tan CH and Chong MS. Sex-specific differences in risk factors for sarcopenia amongst community-dwelling older adults. Age (Dordr) 2015; 37: 121.
[40] Alexopoulos T, Vasilieva L, Kontogianni MD, Tenta R, Georgiou A, Stroumpouli E, Mani I and Alexopoulou A. Myostatin in combination with creatine phosphokinase or albumin may differentiate patients with cirrhosis and sarcopenia. Am J Physiol Gastrointest Liver Physiol 2021; 321: G543-G551.
[41] Kumar A, Davuluri G, Silva RNE, Engelen MPKJ, Ten Have GAM, Prayson R, Deutz NEP and Dasarathy S. Ammonia lowering reverses sarcopenia of cirrhosis by restoring skeletal muscle proteostasis. Hepatology 2017; 65: 2045-2058.
[42] Nishikawa R, Fukuda T, Haruyama A, Shibasaki I, Yamaguchi S, Arikawa T, Obi S, Amano H, Yagi H, Sakuma M, Abe S, Fukuda H, Toyoda S and Nakajima T. Association between serum GDF-15, myostatin, and sarcopenia in cardiovascular surgery patients. Int J Cardiol Heart Vasc 2022; 42: 101114.
[43] Czaja-Stolc S, Chatrenet A, Potrykus M, Ruszkowski J, Torreggiani M, Lichodziejewska-Niemierko M, Dębska-Ślizień A, Piccoli GB and Małgorzewicz S. Adipokines and myokines as markers of malnutrition and sarcopenia in patients receiving kidney replacement therapy: an observational, cross-sectional study. Nutrients 2024; 16: 2480.
[44] Oliveira PGS, Schwed JF, Chiuso-Minicucci F, Duarte SRS, Nascimento LM, Dorna MS, Costa NA, Okoshi K, Okoshi MP, Azevedo PS, Polegato BF, Paiva SAR, Zornoff LAM and Minicucci MF. Association between serum myostatin levels, hospital mortality, and muscle mass and strength following ST-elevation myocardial infarction. Heart Lung Circ 2022; 31: 365-371.
[45] Chew J, Tay L, Lim JP, Leung BP, Yeo A, Yew S, Ding YY and Lim WS. Serum myostatin and IGF-1 as gender-specific biomarkers of frailty and low muscle mass in community-dwelling older adults. J Nutr Health Aging 2019; 23: 979-986.
[46] García-Fontana B, Reyes-García R, Morales-Santana S, Ávila-Rubio V, Muñoz-Garach A, Rozas-Moreno P and Muñoz-Torres M. Relationship between myostatin and irisin in type 2 diabetes mellitus: a compensatory mechanism to an unfavourable metabolic state? Endocrine 2016; 52: 54-62.
[47] Zügel M, Qiu S, Laszlo R, Bosnyák E, Weigt C, Müller D, Diel P, Steinacker JM and Schumann U. The role of sex, adiposity, and gonadectomy in the regulation of irisin secretion. Endocrine 2016; 54: 101-110.
[48] Bergen HR 3rd, Farr JN, Vanderboom PM, Atkinson EJ, White TA, Singh RJ, Khosla S and LeBrasseur NK. Myostatin as a mediator of sarcopenia versus homeostatic regulator of muscle mass: insights using a new mass spectrometry-based assay. Skelet Muscle 2015; 5: 21.
[49] Ladang A, Beaudart C, Reginster JY, Al-Daghri N, Bruyère O, Burlet N, Cesari M, Cherubini A, da Silva MC, Cooper C, Cruz-Jentoft AJ, Landi F, Laslop A, Maggi S, Mobasheri A, Ormarsdottir S, Radermecker R, Visser M, Yerro MCP, Rizzoli R and Cavalier E. Biochemical markers of musculoskeletal health and aging to be assessed in clinical trials of drugs aiming at the treatment of sarcopenia: consensus paper from an expert group meeting organized by the European Society for Clinical and Economic As-

pects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) and the Centre Académique de Recherche et d'Expérimentation en Santé (CARES SPRL), under the auspices of the World Health Organization Collaborating Center for the Epidemiology of Musculoskeletal Conditions and Aging. Calcif Tissue Int 2023; 112: 197-217.

[50] Liaw FY, Kao TW, Fang WH, Han DS, Chi YC and Yang WS. Increased follistatin associated with decreased gait speed among old adults. Eur J Clin Invest 2016; 46: 321-327.

[51] Hofmann M, Halper B, Oesen S, Franzke B, Stuparits P, Tschan H, Bachl N, Strasser EM, Quittan M, Ploder M, Wagner KH and Wessner B. Serum concentrations of insulin-like growth factor-1, members of the TGF-beta superfamily and follistatin do not reflect different stages of dynapenia and sarcopenia in elderly women. Exp Gerontol 2015; 64: 35-45.

[52] Ratkevicius A, Joyson A, Selmer I, Dhanani T, Grierson C, Tommasi AM, DeVries A, Rauchhaus P, Crowther D, Alesci S, Yaworsky P, Gilbert F, Redpath TW, Brady J, Fearon KC, Reid DM, Greig CA and Wackerhage H. Serum concentrations of myostatin and myostatin-interacting proteins do not differ between young and sarcopenic elderly men. J Gerontol A Biol Sci Med Sci 2011; 66: 620-626.

[53] Jiang C, Wang Y, Fu W, Zhang G, Feng X, Wang X, Wang F, Zhang L and Deng Y. Association between sarcopenia and prognosis of hepatocellular carcinoma: a systematic review and meta-analysis. Front Nutr 2022; 9: 978110.

[54] Aryana IGPS, Putrawan IBP, Purnami NKR, Kuswardhani RAT and Astika IN. The relationship between follistatin and sarcopenia in elderly. Indones J Biomed Sci 2022; 16: 86-90.

[55] Schwanke CH, Margutti KM, Costodio AR, Schuch NJ and Daroncho M. Sarcopenia prevalence according to different muscle mass assessment methods in dwelling elderly. Innovation in Aging 2017; 1 Suppl 1: 772-773.

[56] Lage VKDS, de Paula FA, Lima LP, Santos JNV, Dos Santos JM, Viegas ÂA, da Silva GP, de Almeida HC, Rodrigues ALDSNT, Leopoldino AAO, de Avelar NCP, Danielewicz AL, Parentoni AN, Teixeira AL, Oliveira MX, Lacerda ACR and Mendonça VA. Plasma levels of myokines and inflammatory markers are related with functional and respiratory performance in older adults with COPD and sarcopenia. Exp Gerontol 2022; 164: 111834.

[57] Miyazaki S, Iino N, Koda R, Narita I and Kaneko Y. Brain-derived neurotrophic factor is associated with sarcopenia and frailty in Japanese hemodialysis patients. Geriatr Gerontol Int 2021; 21: 27-33.

[58] Elliott JE, Greising SM, Mantilla CB and Sieck GC. Functional impact of sarcopenia in respiratory muscles. Respir Physiol Neurobiol 2016; 226: 137-146.

[59] Arosio B, Calvani R, Ferri E, Coelho-Junior HJ, Carandina A, Campanelli F, Ghiglieri V, Marzetti E and Picca A. Sarcopenia and cognitive decline in older adults: targeting the muscle-brain axis. Nutrients 2023; 15: 1853.

[60] Moreira-Pais A, Ferreira R, Oliveira PA and Duarte JA. A neuromuscular perspective of sarcopenia pathogenesis: deciphering the signaling pathways involved. Geroscience 2022; 44: 1199-1213.

[61] Koito Y, Yanishi M, Kimura Y, Tsukaguchi H, Kinoshita H and Matsuda T. Serum brain-derived neurotrophic factor and myostatin levels are associated with skeletal muscle mass in kidney transplant recipients. Transplant Proc 2021; 53: 1939-1944.

[62] Karim A, Muhammad T and Qaisar R. Prediction of sarcopenia using multiple biomarkers of neuromuscular junction degeneration in chronic obstructive pulmonary disease. J Pers Med 2021; 11: 919.

[63] Karim A, Iqbal MS, Muhammad T and Qaisar R. Evaluation of sarcopenia using biomarkers of the neuromuscular junction in Parkinson's disease. J Mol Neurosci 2022; 72: 820-829.

[64] Wei YC, Wang SR and Xu XH. Sex differences in brain-derived neurotrophic factor signaling: functions and implications. J Neurosci Res 2017; 95: 336-344.

[65] Håkansson K, Ledreux A, Daffner K, Terjestam Y, Bergman P, Carlsson R, Kivipelto M, Winblad B, Granholm AC and Mohammed AK. BDNF responses in healthy older persons to 35 minutes of physical exercise, cognitive training, and mindfulness: associations with working memory function. J Alzheimers Dis 2017; 55: 645-657.