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From Muscle Contraction to Systemic Health: The Emerging Role of Myokines

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Abstract

Background.

Skeletal muscle is increasingly recognized as a metabolically active endocrine and paracrine organ capable of communicating with distant tissues through a diverse secretome. Exercise-induced myokines have been proposed as important mediators of the systemic effects of physical activity, although the strength of evidence differs substantially between individual molecules.

Aim.

The aim of this narrative review was to summarize current evidence regarding the endocrine function of skeletal muscle, the biological characteristics of major myokines, exercise-induced changes in myokine signaling, muscle–organ crosstalk, and the potential relevance of myokines to chronic diseases and therapeutic development.

Material and methods.

A narrative literature review was performed using PubMed, Scopus, and Web of Science. Publications published between January 2015 and June 2026 were considered, together with

selected earlier landmark studies. The search focused on skeletal muscle endocrine function, myokine biology, exercise physiology, inter-organ communication, metabolic diseases, and potential clinical applications.

Results.

Skeletal muscle releases a heterogeneous group of signaling molecules whose expression and secretion are influenced by exercise modality, intensity, duration, training status, nutritional state, and metabolic health. Interleukin-6 and myostatin are among the best-characterized muscle-derived signaling factors. Other molecules, including irisin, interleukin-15, brain-derived neurotrophic factor, fibroblast growth factor 21, SPARC, apelin, and meteorin-like protein, have also been investigated, although evidence regarding their muscle origin and physiological significance in humans is more heterogeneous. Myokine-related signaling has been implicated in glucose and lipid metabolism, adipose tissue biology, cardiovascular function, bone remodeling, immune regulation, and muscle–brain communication.

Conclusions.

Skeletal muscle endocrine activity provides an important mechanistic framework for understanding the systemic effects of physical activity. However, substantial heterogeneity in study populations, exercise protocols, biological sampling, and analytical methods limits the translation of experimental findings into clinical practice. Further well-designed human studies and standardized analytical approaches are required to establish the diagnostic and therapeutic value of individual myokines.

Keywords: skeletal muscle; myokines; endocrine organ; exercise; physical activity; muscle secretome; inter-organ communication; chronic diseases; exercise physiology

1. Introduction

Skeletal muscle is increasingly recognized as a metabolically active endocrine organ whose functions extend beyond its traditional roles in locomotion, posture, and energy storage. In response to muscle contraction, skeletal muscle releases a variety of biologically active molecules, collectively referred to as myokines, which participate in autocrine, paracrine, and endocrine signaling and facilitate communication between skeletal muscle and distant organs.

The identification of interleukin-6 (IL-6) as an exercise-induced myokine was a landmark finding that contributed to the development of the concept of skeletal muscle as an endocrine organ (Pedersen and Febbraio, 2008; Febbraio and Pedersen, 2005).

The skeletal muscle secretome includes numerous cytokines, peptides, and other signaling molecules, including IL-6, irisin, myostatin, interleukin-15 (IL-15), brain-derived neurotrophic factor (BDNF), and fibroblast growth factor 21 (FGF21). Their secretion is influenced by exercise modality, intensity, duration, training status, and metabolic conditions. Through muscle–organ communication, myokines may contribute to the regulation of glucose and lipid metabolism, inflammatory responses, tissue adaptation, and systemic metabolic homeostasis (Severinsen and Pedersen, 2020; Whitham and Febbraio, 2016).

Alterations in myokine signaling have also been associated with metabolic and chronic diseases, including obesity, type 2 diabetes mellitus, cardiovascular disease, sarcopenia, and neurodegenerative disorders. However, the biological and clinical significance of individual myokines remains incompletely established, particularly in humans. Differences in study populations, exercise protocols, analytical methods, and biomarker assessment contribute to considerable heterogeneity across studies and limit the translation of experimental findings into clinical practice (Eckel, 2019; Severinsen and Pedersen, 2020).

This narrative review summarizes current evidence on the endocrine function of skeletal muscle, with particular emphasis on major myokines, exercise-induced adaptations, muscle–organ communication, and their potential relevance to human health and chronic disease. Current limitations of the available evidence and future therapeutic perspectives are also discussed.

2. Methods

This study was conducted as a narrative literature review aimed at summarizing current evidence on the endocrine function of skeletal muscle and the biological role of myokines in exercise physiology and chronic diseases.

A literature search was performed using the PubMed, Scopus, and Web of Science databases. Studies published between January 2015 and June 2026 were considered. In addition, selected

earlier publications of fundamental scientific importance, including landmark studies establishing the concept of skeletal muscle as an endocrine organ, were included.

The search strategy combined Medical Subject Headings (MeSH), database-specific indexing terms, and free-text keywords using the Boolean operators AND and OR. The main search terms included “myokines,” “skeletal muscle,” “endocrine organ,” “exercise,” “physical activity,” “muscle secretome,” “interleukin-6,” “IL-15,” “irisin,” “myostatin,” “brain-derived neurotrophic factor,” “fibroblast growth factor 21,” “secreted protein acidic and rich in cysteine,” and “exercise adaptations.”

Eligible publications included original research articles, systematic reviews, and meta-analyses published in English. Publications were considered eligible when they were relevant to the objectives of the review and provided sufficient scientific information on myokine biology, skeletal muscle endocrine function, exercise-induced adaptations, inter-organ communication, or potential clinical applications. Conference abstracts, editorials, letters to the editor, case reports, and publications not directly related to the subject of the review were excluded.

The selected literature was analyzed with particular emphasis on the mechanisms of myokine synthesis and secretion, the effects of different forms of physical activity, muscle–organ communication, physiological adaptations to exercise, and the potential involvement of myokines in chronic diseases. Particular attention was also given to the potential use of myokines as biomarkers and therapeutic targets.

As this was a narrative review, no formal systematic-review risk-of-bias assessment or quantitative meta-analysis was performed.

3. Skeletal Muscle as an Endocrine Organ

Skeletal muscle is increasingly recognized as a metabolically active endocrine and paracrine organ whose physiological functions extend beyond locomotion, maintenance of posture, thermogenesis, and protein storage. In response to muscle contraction and metabolic stimuli, skeletal muscle produces and releases a broad range of signaling molecules, collectively referred to as myokines. These factors may act through autocrine, paracrine, and endocrine

mechanisms and contribute to communication between skeletal muscle and other tissues (Pedersen and Febbraio, 2008; Severinsen and Pedersen, 2020).

The concept of skeletal muscle as an endocrine organ emerged from observations demonstrating that physical exercise induces the release of interleukin-6 (IL-6) from contracting skeletal muscle. This finding provided an important basis for the development of the myokine concept and stimulated extensive research into the skeletal muscle secretome (Pedersen and Febbraio, 2008; Pedersen and Febbraio, 2012). Subsequent advances in proteomics, transcriptomics, and molecular biology have identified a large and continuously expanding number of candidate muscle-derived signaling molecules. However, the identification of a molecule within the muscle secretome does not necessarily demonstrate that it functions as a physiologically relevant endocrine mediator in humans.

Myokine expression and secretion are influenced by multiple physiological and metabolic factors, including exercise modality, intensity, duration, training status, age, nutritional status, muscle mass, and metabolic health. Exercise-induced changes in intracellular energy status activate signaling pathways involving AMP-activated protein kinase (AMPK), mitogen-activated protein kinases (MAPKs), and peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α). These pathways regulate transcriptional and post-transcriptional responses to exercise and may contribute to changes in the skeletal muscle secretome (Karstoft and Pedersen, 2016; Severinsen and Pedersen, 2020).

Muscle-derived signaling molecules may influence tissues including adipose tissue, liver, bone, cardiovascular tissues, and the nervous system. Such interactions are commonly described as muscle–organ crosstalk and provide a potential molecular framework for understanding how physical activity can induce systemic physiological adaptations. Nevertheless, the strength of evidence differs substantially between individual signaling molecules. Some myokines, particularly IL-6 and myostatin, have been relatively extensively characterized, whereas the physiological significance of several proposed myokines remains uncertain, particularly in humans (Whitham and Febbraio, 2016; Severinsen and Pedersen, 2020).

Importantly, skeletal muscle should not be considered an isolated endocrine system. Its secretory activity forms part of a broader network involving adipokines, hepatokines, osteokines, cytokines, metabolites, and extracellular vesicles derived from multiple tissues.

Consequently, exercise-induced systemic effects are likely to result from coordinated inter-organ signaling rather than from the action of individual myokines alone.

Overall, current evidence supports the concept of skeletal muscle as an important endocrine and paracrine organ. However, distinguishing established physiological effects from experimental or predominantly preclinical observations remains essential. Further well-controlled human studies are required to determine the extent to which individual myokines contribute causally to exercise adaptation and disease prevention.

4. Myokines: Biological Characteristics and Mechanisms of Action

Myokines comprise a heterogeneous group of signaling molecules associated with skeletal muscle, including cytokines, peptides, growth factors, metabolites, and other mediators released or regulated by skeletal muscle in response to contraction and metabolic stimuli. They may participate in autocrine, paracrine, and endocrine signaling and contribute to communication between skeletal muscle and other tissues (Whitham and Febbraio, 2016; Severinsen and Pedersen, 2020).

The term “myokine” should, however, be interpreted with caution. The detection of a signaling molecule in skeletal muscle or in muscle cell culture does not by itself establish that the molecule is secreted by skeletal muscle in physiologically relevant concentrations in humans or that it exerts a systemic endocrine effect. This distinction is particularly important for molecules such as irisin, BDNF, FGF21, and IL-15, for which experimental findings and human data are not always consistent.

The production and release of muscle-derived signaling molecules are regulated by the metabolic and mechanical demands imposed on skeletal muscle. During exercise, changes in cellular energy status and intracellular signaling activate pathways involving AMPK, MAPKs, PGC-1α, and other exercise-responsive regulators. These pathways influence gene transcription, protein synthesis, mitochondrial adaptation, and the release of signaling molecules (Karstoft and Pedersen, 2016; Severinsen and Pedersen, 2020).

The biological effects of myokines may occur at different levels. Autocrine signaling may influence skeletal muscle metabolism, mitochondrial function, protein turnover, and tissue

remodeling. Paracrine signaling may affect neighboring endothelial, stromal, immune, and muscle cells. Endocrine signaling involves the release of factors into the circulation and their potential effects on distant organs. Together, these processes contribute to the concept of muscle–organ crosstalk.

IL-6 represents one of the best-characterized examples of an exercise-responsive muscle-derived signaling molecule. During prolonged exercise, circulating IL-6 concentrations can increase substantially, with the magnitude of the response influenced by exercise duration, intensity, and intramuscular glycogen availability. Exercise-associated IL-6 signaling differs from the sustained inflammatory response observed in many pathological conditions and has been implicated in the regulation of substrate availability and energy metabolism during exercise (Pedersen and Febbraio, 2008; Carey and Febbraio, 2004).

Other proposed myokines have demonstrated more heterogeneous evidence. Irisin, a peptide derived from fibronectin type III domain-containing protein 5 (FNDC5), has attracted considerable interest because of experimental evidence linking the PGC-1α/FNDC5 pathway to adipose tissue metabolism. Experimental studies have suggested a role for irisin in the induction of brown-fat-like characteristics in white adipose tissue. However, substantial methodological variability in the measurement of circulating irisin and inconsistencies between human studies limit definitive conclusions regarding its physiological importance (Boström et al., 2012; Perakakis et al., 2017).

Myostatin, also known as growth differentiation factor-8 (GDF-8), belongs to the transforming growth factor-beta (TGF-β) superfamily and represents a well-established negative regulator of skeletal muscle growth. It influences satellite cell activity and muscle protein turnover and has consequently been investigated in relation to muscle hypertrophy, sarcopenia, immobilization, and muscle-wasting disorders (Egerman and Glass, 2014).

IL-15 has been investigated in relation to skeletal muscle mass and adipose tissue metabolism. Experimental evidence suggests that IL-15 may influence muscle protein metabolism and body composition; however, findings concerning exercise-induced changes in circulating IL-15 concentrations remain inconsistent. Similarly, BDNF is predominantly associated with the central nervous system, although it is also detected in skeletal muscle. Its role in exercise-related neuroplasticity is well supported, but the extent to which skeletal muscle-derived BDNF

directly mediates systemic effects of exercise remains uncertain (Wrann et al., 2013; Severinsen and Pedersen, 2020).

FGF21 provides another example of the importance of distinguishing muscle-associated signaling from muscle-specific endocrine secretion. FGF21 is produced by several tissues, particularly the liver, and therefore should not be considered an exclusively skeletal muscle-derived myokine. Nevertheless, skeletal muscle may participate in the regulation of FGF21-related metabolic signaling under specific physiological conditions (Fisher and Maratos-Flier, 2016).

Taken together, current evidence indicates that the skeletal muscle secretome represents a complex and dynamic signaling network rather than a collection of isolated endocrine factors. The physiological relevance of individual molecules varies considerably, and the available evidence is strongest for selected factors such as IL-6 and myostatin. Future research should prioritize well-designed human studies using standardized analytical methods to determine the causal contribution of individual myokines to exercise adaptation and systemic health.

5. Major Myokines

5.1. Interleukin-6 (IL-6)

Interleukin-6 (IL-6) was among the first exercise-induced myokines to be identified and remains the most extensively investigated component of the muscle secretome. In contrast to IL-6 produced by immune cells during inflammatory responses, skeletal muscle-derived IL-6 primarily exerts metabolic rather than pro-inflammatory effects. During prolonged endurance exercise, circulating IL-6 concentrations may increase substantially, with the magnitude of this response depending on exercise duration, intensity, and intramuscular glycogen availability (Pedersen and Febbraio, 2008; Pedersen, 2009).

Exercise-induced IL-6 enhances glucose uptake by skeletal muscle through activation of AMP-activated protein kinase (AMPK), stimulates fatty acid oxidation, and promotes hepatic glucose production, thereby contributing to energy homeostasis during prolonged exercise. Furthermore, muscle-derived IL-6 may exert anti-inflammatory effects by stimulating the production of interleukin-10 (IL-10) and interleukin-1 receptor antagonist (IL-1ra) while

suppressing tumor necrosis factor-alpha (TNF-α). These biological characteristics distinguish exercise-induced IL-6 from its role in chronic inflammatory conditions and emphasize its importance in metabolic regulation (Pedersen and Febbraio, 2008; Carey and Febbraio, 2004).

5.2. Irisin

Irisin is a peptide derived from fibronectin type III domain-containing protein 5 (FNDC5) and has been investigated extensively as a potential mediator of exercise-induced muscle–adipose tissue communication. Experimental studies have suggested that activation of the PGC-1α/FNDC5 pathway may increase irisin-related signaling and promote changes in white adipose tissue, including increased expression of uncoupling protein 1 (UCP1). These findings have generated considerable interest in the potential role of irisin in thermogenesis, energy expenditure, and metabolic regulation (Boström et al., 2012).

However, evidence from human studies remains heterogeneous. Differences in analytical methods, assay specificity, study populations, exercise protocols, and circulating irisin concentrations have contributed to inconsistent findings regarding its relationship with physical activity, obesity, insulin sensitivity, and metabolic health. Therefore, although irisin remains a promising candidate mediator of exercise-induced metabolic adaptations, its precise physiological significance and clinical utility in humans have not yet been definitively established (Perakakis et al., 2017; Severinsen and Pedersen, 2020).

5.3. Myostatin

Myostatin, also known as growth differentiation factor-8 (GDF-8), belongs to the transforming growth factor-beta (TGF-β) superfamily and functions as an important negative regulator of skeletal muscle growth. It regulates satellite cell activity and muscle protein turnover, thereby contributing to the control of skeletal muscle mass. Alterations in myostatin signaling have been investigated in individuals with sarcopenia, prolonged immobilization, and several chronic diseases associated with muscle wasting (Egerman and Glass, 2014; Das et al., 2020).

Regular physical activity, particularly resistance exercise, has been associated with changes in myostatin expression and signaling, although the magnitude and direction of these responses may vary depending on exercise characteristics and study population. Pharmacological inhibition of myostatin-related pathways has therefore emerged as a potential therapeutic

strategy for sarcopenia, cachexia, and other muscle-wasting disorders. However, clinical evidence remains heterogeneous, and further studies are required to establish the long-term efficacy and safety of such approaches (Das et al., 2020).

5.4. Brain-Derived Neurotrophic Factor (BDNF)

Brain-derived neurotrophic factor (BDNF) is a neurotrophin involved in neuronal survival, differentiation, synaptic plasticity, and cognitive function. Although BDNF is expressed predominantly within the central nervous system, it has also been detected in skeletal muscle and has been investigated as a potential component of the molecular pathways linking physical activity with brain function.

Experimental studies have demonstrated that exercise can activate pathways involving PGC-1α and FNDC5 and may increase BDNF-related signaling in the brain. In addition, exercise is associated with changes in circulating BDNF concentrations. These observations provide a potential biological basis for the association between physical activity and neuroplasticity; however, the contribution of skeletal muscle-derived BDNF to systemic and central effects of exercise remains incompletely established (Wrann et al., 2013; Sleiman et al., 2016).

Therefore, BDNF should be considered a potential mediator of muscle–brain communication rather than an exclusively muscle-derived endocrine factor. Further human studies are required to clarify the relative contribution of peripheral and central BDNF sources and their relevance to exercise-induced cognitive and neuroprotective effects (Severinsen and Pedersen, 2020).

5.5. Interleukin-15 (IL-15)

Interleukin-15 (IL-15) is a muscle-associated signaling molecule that has been investigated in relation to skeletal muscle mass and adipose tissue metabolism. Experimental studies suggest that IL-15 may exert anabolic effects on skeletal muscle and may influence muscle protein metabolism. In parallel, IL-15 has been implicated in the regulation of adipose tissue accumulation, suggesting a potential role in the regulation of body composition (Das et al., 2020; Severinsen and Pedersen, 2020).

Experimental evidence indicates that resistance exercise may increase IL-15 expression within skeletal muscle. However, findings regarding exercise-induced changes in circulating IL-15 concentrations remain inconsistent, probably because of differences in study populations,

exercise protocols, sampling conditions, and analytical methodologies. Therefore, additional well-designed human studies are needed to clarify the physiological significance of IL-15 and its potential clinical applications in exercise adaptation and metabolic health (Das et al., 2020).

6. Effects of Physical Activity on Myokine Secretion

Physical activity represents an important physiological stimulus for changes in the skeletal muscle secretome. The endocrine response to exercise is not uniform and depends on exercise modality, intensity, duration, training status, age, nutritional status, muscle mass, and metabolic health (Pedersen and Febbraio, 2012; Severinsen and Pedersen, 2020).

During exercise, increased metabolic demand alters intracellular energy status and activates signaling pathways involving AMPK, MAPKs, and PGC-1α. These pathways contribute to transcriptional regulation and cellular adaptation and may influence the expression and release of muscle-derived signaling molecules. Importantly, acute responses to a single exercise session should be distinguished from chronic adaptations induced by repeated training.

One of the most consistently described exercise-associated responses is the increase in circulating IL-6 during prolonged endurance exercise. The magnitude of this response is influenced by exercise duration, intensity, and intramuscular glycogen availability. Exercise-induced IL-6 has been implicated in the regulation of substrate availability and energy metabolism during prolonged physical activity (Pedersen et al., 2003; Pedersen and Febbraio, 2012).

Resistance exercise induces a partially different molecular response and has been associated with changes in signaling pathways involved in muscle hypertrophy, remodeling, and protein turnover. Changes in myostatin signaling and expression of muscle-associated factors such as IL-15 and decorin have been investigated in relation to these adaptations. However, the magnitude and direction of responses vary between studies, and a simple classification of individual myokines according to exercise modality is not supported by current evidence (Kanzleiter et al., 2014; Das et al., 2020).

Recent evidence from a systematic review and meta-analysis indicates that both aerobic and resistance exercise can modify circulating concentrations of selected myokines, although the

magnitude and direction of these responses are highly dependent on the individual myokine and the timing of biological sampling. The available evidence also suggests that acute exercise-related changes may be most apparent immediately after exercise and during the first hour of recovery, with concentrations of some myokines tending to return toward baseline during subsequent recovery periods. However, substantial heterogeneity between studies limits the ability to draw precise conclusions regarding the effects of specific exercise modalities (Bettariga et al., 2024).

High-intensity interval training may also induce substantial acute changes in selected exercise-responsive signaling molecules. However, although studies have reported changes in IL-6, irisin, and BDNF following high-intensity exercise, the clinical and physiological interpretation of these responses remains limited by methodological heterogeneity and differences in study populations and exercise protocols.

Importantly, exercise-induced myokine responses may differ between healthy individuals and people with metabolic disease or advanced age. Obesity, insulin resistance, and aging have been associated with alterations in muscle endocrine signaling, although the direction and clinical significance of these changes are not uniform across individual myokines. Regular physical activity may modify these signaling responses, but further longitudinal human studies are required to determine whether such changes directly mediate improvements in metabolic and functional health.

Overall, available evidence supports the concept that physical activity modifies skeletal muscle endocrine signaling. Nevertheless, the magnitude and clinical relevance of these responses remain highly dependent on the specific molecule, exercise stimulus, timing of sampling, and characteristics of the individual. Future research should therefore focus on standardized exercise protocols, repeated biological sampling, and clinically meaningful outcomes rather than isolated measurements of circulating myokines.

7. The Role of Myokines in Human Health

Myokines play a fundamental role in maintaining whole-body homeostasis by regulating metabolic, immunological, regenerative, and neuroprotective processes. Secreted by contracting skeletal muscle, these signaling molecules mediate communication between

skeletal muscle and distant organs, including adipose tissue, the liver, pancreas, heart, bone, and the central nervous system. Consequently, the physiological benefits of physical activity extend far beyond local muscular adaptations, inducing systemic responses that contribute to the prevention and management of numerous chronic diseases (Pedersen and Febbraio, 2012; Severinsen and Pedersen, 2020).

7.1. Myokines and Glucose Homeostasis

One of the best-established physiological functions of myokines is the regulation of glucose metabolism. Among these molecules, interleukin-6 (IL-6) has been investigated most extensively because its secretion increases rapidly during physical exercise. Muscle-derived IL-6 enhances glucose uptake by skeletal muscle through activation of AMP-activated protein kinase (AMPK) and promotes the translocation of glucose transporter type 4 (GLUT4) to the cell membrane. Furthermore, IL-6 stimulates fatty acid oxidation and supports glucose homeostasis during prolonged exercise by maintaining adequate substrate availability (Pedersen and Febbraio, 2008; Carey and Febbraio, 2004).

Regular physical activity also improves insulin sensitivity, an effect mediated, at least in part, by exercise-induced myokines acting on insulin signaling pathways. These adaptations contribute substantially to the prevention and management of type 2 diabetes mellitus and metabolic syndrome, emphasizing the endocrine function of skeletal muscle as a key determinant of metabolic health (Severinsen and Pedersen, 2020; Gleeson et al., 2011).

7.2. Myokines and Adipose Tissue

Endocrine communication between skeletal muscle and adipose tissue represents one of the most extensively investigated aspects of muscle–adipose crosstalk. Irisin is among the best-characterized myokines involved in this process. By inducing the expression of uncoupling protein 1 (UCP1), irisin promotes the browning of white adipose tissue, thereby increasing thermogenesis and whole-body energy expenditure. These metabolic adaptations may contribute to the prevention of obesity and obesity-related metabolic disorders (Boström et al., 2012).

Similarly, interleukin-15 (IL-15) has been implicated in the regulation of body composition through its ability to enhance fatty acid oxidation while limiting adipose tissue accumulation

and preserving skeletal muscle mass. Altered secretion of these myokines has been observed in individuals with obesity and insulin resistance, suggesting an important role in the pathophysiology of metabolic diseases (Quinn, 2008; Pedersen and Febbraio, 2012).

7.3. Myokines and Cardiovascular Health

Growing evidence indicates that myokines exert multiple cardioprotective effects and contribute to the maintenance of cardiovascular health. Experimental and clinical studies have demonstrated that exercise-induced myokines may improve endothelial function, increase nitric oxide bioavailability, reduce oxidative stress, and attenuate chronic low-grade inflammation, all of which are recognized contributors to the development of atherosclerosis and cardiovascular disease (Garneau and Aguer, 2019; Severinsen and Pedersen, 2020).

Regular physical activity enhances the secretion and activity of signaling molecules involved in cardiovascular protection, leading to improvements in vascular function and contributing to the reduction of cardiovascular risk. These findings provide important mechanistic insight into the well-established association between habitual exercise and reduced cardiovascular risk (Garneau and Aguer, 2019; Pedersen, 2009).

7.4. Myokines and the Central Nervous System

The interaction between skeletal muscle and the brain has become one of the fastest-growing areas of myokine research. Brain-derived neurotrophic factor (BDNF) is considered an important mediator of muscle–brain communication. Exercise-induced increases in BDNF-related signaling have been associated with neurogenesis, neuronal differentiation, and synaptic plasticity, thereby potentially contributing to learning, memory, and cognitive function (Wrann et al., 2013; Severinsen and Pedersen, 2020).

Recent research has further emphasized the potential role of exercise-induced myokines in muscle–brain crosstalk. Experimental studies have investigated BDNF, irisin, IL-6, insulin-like growth factor-1 (IGF-1), and cathepsin B as possible mediators of communication between skeletal muscle and the central nervous system. However, much of the mechanistic evidence remains derived from experimental models, and the relative contribution of skeletal muscle-derived factors to human brain function remains incompletely established (Kostka et al., 2024).

Accumulating evidence further indicates that regular physical activity is associated with a reduced risk of cognitive decline and neurodegenerative disorders. These neuroprotective effects are likely multifactorial and may involve BDNF-related signaling, improved cerebral perfusion, attenuation of neuroinflammatory processes, metabolic adaptations, and enhanced neuronal resilience. Importantly, the precise contribution of individual myokines remains uncertain, and muscle–brain communication is likely to involve a complex network of

endocrine factors rather than a single signaling molecule (Kostka et al., 2024; Sleiman et al., 2016).

Therefore, myokine-mediated muscle–brain communication should currently be regarded as a promising mechanistic framework rather than an established therapeutic pathway. Further well-designed human studies are required to determine the tissue origin, circulating dynamics, receptor-mediated actions, and clinical relevance of individual exercise-responsive factors.

7.5. Myokines and Bone Metabolism

Skeletal muscle and bone constitute an integrated functional unit that communicates not only through mechanical loading but also via endocrine signaling. Myokines influence bone-forming and bone-resorbing processes and may therefore contribute to the regulation of bone remodeling and skeletal homeostasis. Exercise-induced myokine signaling has been associated with effects on bone formation and may contribute to the maintenance of bone health (Hamrick, 2011; Severinsen and Pedersen, 2020).

The physiological relevance of muscle–bone crosstalk is particularly evident in older adults, in whom the coexistence of sarcopenia and osteoporosis substantially increases the risk of falls, fragility fractures, disability, and loss of independence. Consequently, preservation of skeletal muscle endocrine function may represent an important component of strategies aimed at maintaining musculoskeletal health throughout aging (Hamrick, 2011; Severinsen and Pedersen, 2020).

7.6. Myokines and the Immune System

The beneficial effects of physical activity on immune function are mediated, to a considerable extent, by exercise-induced myokines. Muscle-derived IL-6 stimulates the production of anti-inflammatory cytokines, including interleukin-10 (IL-10) and interleukin-1 receptor antagonist (IL-1ra), while suppressing the synthesis of tumor necrosis factor-alpha (TNF-α). Through these mechanisms, regular exercise may attenuate chronic low-grade inflammation, a hallmark of obesity, type 2 diabetes mellitus, atherosclerosis, and numerous other chronic non-communicable diseases (Pedersen and Febbraio, 2008; Gleeson et al., 2011).

Long-term engagement in regular physical activity has consistently been associated with improved immune regulation and a reduced risk of chronic disease. Both epidemiological and

experimental evidence support the concept that exercise-induced modulation of the muscle secretome contributes to maintaining immune homeostasis and reducing systemic inflammatory burden (Gleeson et al., 2011; Pedersen, 2009).

Overall, myokines have emerged as central regulators of systemic homeostasis, linking skeletal muscle activity with the function of multiple organs and physiological systems. Through their coordinated effects on metabolism, immune regulation, cardiovascular physiology, bone remodeling, and neurobiology, myokines provide a mechanistic basis for many of the health-promoting effects of regular physical activity. Nevertheless, despite substantial advances in understanding myokine biology, many mechanisms underlying tissue-specific actions, inter-organ signaling, and long-term clinical relevance remain incompletely understood. Future translational and clinical studies are therefore essential to clarify their diagnostic and therapeutic potential and to facilitate the development of personalized exercise-based interventions and myokine-targeted therapies (Severinsen and Pedersen, 2020).

8. The Role of Myokines in Selected Diseases

Growing evidence indicates that dysregulated myokine secretion contributes to the pathophysiology of numerous chronic diseases. Altered circulating concentrations and impaired signaling of specific myokines have been reported in patients with obesity, type 2 diabetes mellitus, cardiovascular diseases, sarcopenia, and neurodegenerative disorders. Consequently, myokines are increasingly recognized not only as mediators of exercise-induced adaptations but also as potential biomarkers of metabolic health and disease-related processes and as possible therapeutic targets (Severinsen and Pedersen, 2020; Pedersen and Febbraio, 2012).

8.1. Obesity and Metabolic Syndrome

Obesity is a chronic metabolic disorder characterized by excessive adipose tissue accumulation and persistent low-grade systemic inflammation. In individuals with obesity, the physiological balance between adipokines derived from adipose tissue and myokines secreted by skeletal muscle becomes disrupted, contributing to insulin resistance, oxidative stress, chronic inflammation, and an increased risk of cardiovascular complications (Pedersen and Febbraio, 2012; Kahn et al., 2006).

Regular physical activity enhances the secretion of several metabolically relevant myokines, including irisin, IL-6, and IL-15, which are involved in the regulation of glucose and lipid metabolism and whole-body energy expenditure. Among these, irisin has attracted particular attention because of its ability to induce the browning of white adipose tissue through upregulation of uncoupling protein 1 (UCP1), thereby promoting thermogenesis and increasing energy expenditure. This mechanism may contribute to body weight regulation and metabolic homeostasis (Boström et al., 2012; Perakakis et al., 2017).

Beyond their direct metabolic effects, exercise-induced myokines may also contribute to attenuation of the chronic inflammatory state associated with obesity, further supporting their role as mediators linking skeletal muscle activity with metabolic health. Nevertheless, the precise contribution of individual myokines to obesity pathogenesis and treatment remains incompletely understood, warranting further mechanistic and clinical investigation (Severinsen and Pedersen, 2020; Pedersen and Febbraio, 2012).

8.2. Type 2 Diabetes Mellitus

One of the most thoroughly documented physiological functions of myokines is the regulation of glucose homeostasis. Exercise-induced IL-6 activates AMP-activated protein kinase (AMPK) and contributes to enhanced glucose uptake by skeletal muscle. IL-6 also promotes fatty acid oxidation and participates in the regulation of hepatic glucose production during exercise, thereby contributing to metabolic adaptation to physical activity (Pedersen and Febbraio, 2008; Carey and Febbraio, 2004).

Additional myokines, including irisin and fibroblast growth factor 21 (FGF21), also contribute to glucose and lipid homeostasis. Altered circulating concentrations of these molecules have been reported in individuals with metabolic dysfunction, although the clinical significance of these changes remains uncertain. It remains unclear whether alterations in myokine concentrations represent causal mechanisms in the development of metabolic disease or secondary consequences of insulin resistance and metabolic dysfunction, highlighting the need for further mechanistic, longitudinal, and interventional studies (Perakakis et al., 2017; Fisher and Maratos-Flier, 2016; Severinsen and Pedersen, 2020).

8.3. Cardiovascular Diseases

Chronic inflammation, endothelial dysfunction, and oxidative stress are central mechanisms underlying the development of atherosclerosis and cardiovascular disease. Exercise-induced myokines may exert cardioprotective effects by modulating inflammatory signaling, improving endothelial function, enhancing nitric oxide bioavailability, and reducing oxidative stress. Collectively, these mechanisms may contribute to improved vascular function and reduced cardiovascular risk (Garneau and Aguer, 2019; Severinsen and Pedersen, 2020).

Regular physical activity also promotes favorable changes in blood pressure, lipid profile, body composition, and cardiorespiratory fitness. Increasing evidence suggests that some of these well-established cardiovascular benefits may be mediated, at least in part, through endocrine signaling originating from contracting skeletal muscle, emphasizing the potential importance of muscle-derived factors in cardiovascular protection (Garneau and Aguer, 2019; Severinsen and Pedersen, 2020).

8.4. Sarcopenia

Sarcopenia is a progressive age-related disorder characterized by the loss of skeletal muscle mass, strength, and physical performance. One of the molecular mechanisms implicated in its development is increased myostatin activity, which inhibits skeletal muscle growth and contributes to impaired maintenance of muscle mass (Egerman and Glass, 2014).

Resistance exercise has been associated with changes in myostatin expression and increased activity of anabolic signaling pathways involved in skeletal muscle hypertrophy. Myokines such as IL-15 and decorin have also been implicated in the regulation of muscle growth and remodeling. These adaptations promote the preservation and improvement of skeletal muscle mass and function and may therefore contribute to delaying the progression of age-related muscle loss (Egerman and Glass, 2014; Kanzleiter et al., 2014; Severinsen and Pedersen, 2020).

8.5. Neurodegenerative Diseases

The concept of a functional muscle–brain axis has emerged as one of the promising areas of contemporary myokine research. Among the molecules involved in this bidirectional communication, brain-derived neurotrophic factor (BDNF) plays an important role in neurogenesis, neuronal survival, synaptic plasticity, and cognitive function. Exercise-induced activation of the PGC-1α/FNDC5 pathway has been associated with increased hippocampal BDNF expression, providing a potential molecular mechanism linking physical activity with brain function (Wrann et al., 2013; Severinsen and Pedersen, 2020).

Recent experimental evidence suggests that several exercise-responsive signaling molecules, including BDNF, irisin, IL-6, IGF-1, and cathepsin B, may participate in muscle–brain communication. Proposed mechanisms include modulation of neuroplasticity, synaptic function, neuroinflammation, and metabolic signaling. However, current evidence is derived predominantly from experimental and preclinical studies, and the exact contribution of skeletal muscle-derived myokines to these processes in humans remains uncertain (Kostka et al., 2024).

Epidemiological studies further demonstrate that regular physical activity is associated with a lower risk of cognitive decline and neurodegenerative disorders. These neuroprotective effects are likely multifactorial and may involve BDNF signaling, improved cerebral perfusion, attenuation of neuroinflammation, and enhanced neuronal resilience. Nevertheless, additional clinical studies are required to determine the extent to which modulation of myokine-related pathways contributes to these effects and whether such pathways can be translated into effective therapeutic interventions for neurodegenerative disorders (Wrann et al., 2013; Sleiman et al., 2016; Kostka et al., 2024).

8.6. Clinical Perspectives

Rapid advances in myokine research have generated considerable interest in their potential clinical applications. Myokines may serve as biomarkers reflecting metabolic health, exercise adaptation, or disease-related processes, while pharmacological modulation of myokine signaling represents a potential strategy for the treatment of chronic diseases. Current experimental approaches include the development of recombinant myokines, myokine analogues, receptor agonists, and interventions capable of stimulating endogenous myokine signaling (Whitham and Febbraio, 2016; Severinsen and Pedersen, 2020).

Despite encouraging preclinical findings, translation into routine clinical practice remains challenging. Many aspects of myokine biology—including tissue-specific actions, receptor interactions, optimal therapeutic dosing, long-term safety, and interindividual variability in treatment response—require further investigation. Therefore, well-designed randomized controlled trials are essential before myokine-based therapies can be incorporated into evidence-based clinical practice (Whitham and Febbraio, 2016).

Overall, myokines have emerged as important molecular mediators linking skeletal muscle activity with systemic health. Their involvement in the regulation of metabolic, cardiovascular, musculoskeletal, and neurobiological processes provides a biological rationale for the use of regular physical activity as both a preventive and therapeutic intervention. Continued advances in translational research may facilitate the development of innovative diagnostic approaches

and targeted therapeutic strategies in metabolic medicine, cardiology, neurology, and geriatric medicine (Severinsen and Pedersen, 2020; Whitham and Febbraio, 2016).

9. Therapeutic Perspectives and Future Research Directions

Rapid advances in myokine research have transformed the perception of these molecules from simple mediators of exercise-induced adaptations into promising biomarkers and potential therapeutic targets. Increasing understanding of the molecular mechanisms regulating myokine synthesis, secretion, and signaling has created new opportunities for the development of targeted interventions for metabolic, cardiovascular, musculoskeletal, and neurodegenerative diseases. Consequently, the skeletal muscle secretome has become an important focus of translational research and precision medicine (Whitham and Febbraio, 2016; Severinsen and Pedersen, 2020).

Recent research has increasingly emphasized the importance of myokine-mediated muscle–organ communication as a potential translational target. Myokines may participate in coordinated signaling between skeletal muscle and metabolically active organs, including adipose tissue, liver, pancreas, cardiovascular tissues, bone, and the brain. However, translation of these mechanisms into clinical interventions remains limited by incomplete understanding of tissue-specific myokine secretion, receptor interactions, temporal dynamics, and interindividual variability (Yi et al., 2025).

One of the most promising areas of investigation is the application of myokines as biomarkers for disease diagnosis, prognosis, and therapeutic monitoring. Circulating concentrations of molecules such as interleukin-6 (IL-6), irisin, brain-derived neurotrophic factor (BDNF), and myostatin have been reported to change in response to physical exercise and in association with metabolic or physiological states. In the future, quantitative assessment of selected myokines may facilitate the monitoring of exercise responses and rehabilitation outcomes and potentially support the optimization of individualized exercise prescriptions and therapeutic interventions. However, the diagnostic and prognostic value of individual myokines requires further validation in well-characterized human populations (Severinsen and Pedersen, 2020; Garneau and Aguer, 2019; Whitham and Febbraio, 2016).

Another major research focus involves the development of pharmacological agents capable of modulating myokine signaling pathways or their receptors. Among the most extensively investigated strategies are myostatin inhibitors, which aim to prevent or reverse skeletal muscle wasting in conditions such as sarcopenia, muscular dystrophies, and cancer cachexia. Although preclinical studies have demonstrated encouraging anabolic effects, clinical trials have produced heterogeneous results, and myostatin-targeted therapies have not yet achieved widespread implementation in routine clinical practice (Rodriguez et al., 2014; Sartori et al., 2013).

Increasing attention has also been directed toward irisin and BDNF because of their potential metabolic and neurobiological effects. Experimental evidence suggests that irisin may influence glucose homeostasis, energy expenditure, and adipose tissue metabolism, although substantial inconsistencies remain regarding its measurement and physiological significance in humans. Likewise, BDNF has emerged as a potential mediator of exercise-related neuroplasticity and neuroprotection. Nevertheless, despite encouraging experimental findings, the long-term efficacy and safety of pharmacological modulation of these pathways remain to be established in large-scale clinical studies (Perakakis et al., 2017; Wrann et al., 2013; Severinsen and Pedersen, 2020).

Recent advances in molecular biology, proteomics, metabolomics, transcriptomics, and single-cell technologies have substantially expanded our understanding of the muscle secretome. High-throughput analytical platforms continue to identify previously unrecognized exercise-responsive signaling molecules, providing new insights into the complex endocrine communication between skeletal muscle and distant organs. These technological developments may accelerate the discovery and validation of novel myokines with potential diagnostic, prognostic, and therapeutic value (Whitham and Febbraio, 2016; Severinsen and Pedersen, 2020).

Despite remarkable progress over the past two decades, several fundamental aspects of myokine biology remain incompletely understood. The precise physiological functions of many newly identified myokines, their tissue-specific actions, receptor interactions, and coordinated signaling networks have yet to be fully elucidated. Furthermore, considerable heterogeneity among published studies—including differences in participant characteristics, exercise modalities, training intensity, intervention duration, biological sampling protocols, and

analytical methodologies—limits direct comparisons across studies and complicates the development of evidence-based clinical recommendations (Whitham and Febbraio, 2016; Severinsen and Pedersen, 2020).

Future research should therefore prioritize well-designed translational, longitudinal, and randomized clinical studies integrating mechanistic investigations with clinically meaningful outcomes. Standardization of experimental protocols, validation of candidate biomarkers, and clarification of dose–response relationships between different exercise modalities and myokine secretion will be essential for translating experimental discoveries into clinical applications. Integration of multi-omics approaches, artificial intelligence, and systems biology may further improve understanding of the complex interactions within the muscle secretome and facilitate the development of personalized exercise medicine.

In summary, myokines represent one of the promising areas of contemporary exercise physiology and molecular medicine. Continued advances in understanding skeletal muscle endocrine function are expected to create new opportunities for disease prevention, monitoring of exercise responses, and potentially targeted treatment of chronic diseases. As research continues to evolve, myokine-based diagnostics and therapeutic strategies may contribute to precision medicine, further reinforcing the central role of physical activity in modern preventive and therapeutic healthcare (Whitham and Febbraio, 2016; Severinsen and Pedersen, 2020).

10. Limitations of Current Research

Despite the rapid expansion of myokine research over the past two decades, current knowledge regarding their biological significance and clinical applicability remains incomplete. A substantial proportion of the available evidence originates from experimental studies, animal models, or observational investigations, whereas large-scale clinical trials involving diverse patient populations remain relatively scarce. Consequently, the precise contribution of individual myokines to disease pathogenesis and their potential role in routine clinical practice have yet to be fully established (Pedersen and Febbraio, 2008; Severinsen and Pedersen, 2020; Das et al., 2020).

One of the major limitations of the current literature is the considerable heterogeneity among published studies. Significant differences exist in exercise protocols, including exercise

modality, intensity, duration, frequency, and training status, as well as in the demographic and clinical characteristics of study participants. Previous investigations have included healthy young adults, older individuals, elite athletes, and patients with obesity, type 2 diabetes mellitus, cardiovascular diseases, or sarcopenia. Such variability complicates direct comparisons across studies and limits the development of robust evidence-based conclusions regarding exercise-induced myokine responses (Severinsen and Pedersen, 2020; Pedersen and Febbraio, 2012).

Another important challenge is the lack of standardized methodologies for measuring circulating myokine concentrations. Different studies employ a wide variety of analytical techniques, immunoassays, laboratory protocols, and biological sampling procedures, resulting in substantial methodological variability. Furthermore, circulating concentrations of many myokines are influenced by numerous physiological factors, including age, sex, circadian rhythm, nutritional status, training status, body composition, and metabolic health. These sources of biological variation further complicate data interpretation and reduce comparability between studies (Whitham and Febbraio, 2016; Severinsen and Pedersen, 2020).

A substantial proportion of current knowledge regarding myokine biology is derived from animal experiments and in vitro cell culture models. Although these approaches have provided valuable mechanistic insights into intracellular signaling pathways and endocrine communication, their findings cannot always be directly translated to human physiology. Consequently, additional well-designed human intervention studies are required to validate experimental observations and determine their clinical relevance (Whitham and Febbraio, 2016; Karstoft and Pedersen, 2016).

The biological significance of several myokines also remains controversial. Irisin represents a notable example, as conflicting findings have been reported regarding its association with obesity, type 2 diabetes mellitus, physical activity, and metabolic health. These inconsistencies are likely attributable, at least in part, to methodological differences, variability in study populations, and differences in assay specificity and sensitivity. The absence of universally accepted analytical standards for irisin quantification further complicates the interpretation and comparison of published results (Perakakis et al., 2017).

Another important limitation is the limited availability of long-term prospective studies. Most published investigations evaluate the acute endocrine response to a single exercise session or the effects of relatively short-term training interventions lasting several weeks or months. In

contrast, longitudinal studies examining the influence of sustained physical activity over years or decades on the muscle secretome and chronic disease prevention remain scarce. Such investigations are essential for understanding the long-term physiological significance of myokine signaling and its contribution to healthy aging (Severinsen and Pedersen, 2020; Das et al., 2020).

Increasing evidence also suggests that myokines should not be considered isolated signaling molecules but rather components of a highly integrated endocrine network involving adipokines, osteokines, hepatokines, and other tissue-derived signaling molecules. However, the complex interactions among these endocrine pathways remain incompletely understood and represent an important area for future investigation (Severinsen and Pedersen, 2020).

Systems biology approaches integrating proteomics, metabolomics, transcriptomics, and multi-omics technologies are expected to provide a more comprehensive understanding of inter-organ communication and metabolic regulation. Such approaches may help identify coordinated patterns of muscle-derived signaling rather than focusing exclusively on individual myokines and may improve the biological interpretation of the muscle secretome (Whitham and Febbraio, 2016; Severinsen and Pedersen, 2020).

Despite these limitations, the available evidence consistently supports the concept that myokines contribute to muscle–organ crosstalk and participate in the regulation of systemic physiological responses to physical activity. Continued advances in molecular biology, high-throughput proteomics, multi-omics technologies, artificial intelligence-assisted data analysis, and translational research may refine our understanding of skeletal muscle endocrine function. Ultimately, these developments may facilitate the identification and validation of novel biomarkers, optimization of individualized exercise interventions, and development of myokine-targeted therapeutic strategies, bringing the field closer to potential implementation within precision and personalized medicine (Whitham and Febbraio, 2016; Severinsen and Pedersen, 2020).

11. Conclusions

Skeletal muscle is now recognized as a highly active endocrine organ that plays a fundamental role in regulating whole-body homeostasis through the synthesis and secretion of myokines. Beyond their local effects on skeletal muscle adaptation, myokines mediate complex endocrine communication between skeletal muscle and multiple organs, including adipose tissue, the liver, pancreas, cardiovascular system, bone, and the central nervous system. Consequently, the beneficial effects of regular physical activity extend far beyond improvements in muscle function, contributing to the maintenance of metabolic health and the prevention of numerous chronic diseases.

Current evidence demonstrates that exercise-induced myokines regulate glucose and lipid metabolism, improve insulin sensitivity, modulate inflammatory responses, promote tissue regeneration, and support cardiovascular and neurological function. These biological properties provide a mechanistic explanation for many of the well-established health benefits of regular physical activity and highlight the central role of skeletal muscle as a key regulator of systemic physiology.

Increasing evidence also suggests that dysregulated myokine secretion contributes to the development and progression of obesity, type 2 diabetes mellitus, cardiovascular diseases, sarcopenia, and neurodegenerative disorders. Accordingly, myokines have emerged as promising biomarkers of metabolic health and attractive therapeutic targets. Nevertheless, despite encouraging experimental and preclinical findings, their translation into routine clinical practice remains limited, and additional high-quality human studies are required to establish their diagnostic accuracy, therapeutic efficacy, and long-term safety.

Future research should focus on standardizing methodologies for myokine assessment, identifying novel exercise-responsive molecules, and clarifying the dose–response relationships between different exercise modalities and endocrine adaptations. Advances in molecular biology, multi-omics technologies, and precision medicine are expected to accelerate the clinical translation of myokine research and facilitate the development of individualized exercise-based interventions and innovative therapeutic strategies.

In conclusion, myokines represent one of the most promising areas of contemporary exercise physiology and molecular medicine. A better understanding of skeletal muscle endocrine function will not only expand our knowledge of the mechanisms underlying exercise-induced health benefits but may also contribute to the development of novel preventive, diagnostic, and therapeutic approaches for chronic diseases, reinforcing the central role of physical activity in modern healthcare.

Disclosure

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The authors declare no conflict of interest.

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