Thematic Section: Advances in Musculoskeletal and Neuromuscular Rehabilitation
Eur J Transl Myol 35 (3) 13365, 2025 doi: 10.4081/ejtm.2025.13365

Impact of myokines on chronic liver diseases: exploring the effects of metabolic dysfunction-associated steatotic liver disease (MASLD) on skeletal muscle. A narrative review

Francisco Aguirre,[1,2,3] Mayalen Valero-Breton,[1,2,3] Daniel Cabrera,[4,5] Luis Peñailillo,[6] María Carolina Otero,[7] Claudia Fredes,[8] Claudio Cabello-Verrugio[1,2,3]

[1]Center for Research on Pandemic Resilience, Faculty of Life Sciences and Institute of Public Health, Universidad Andres Bello, Santiago, Chile; [2]Laboratory of Muscle Pathology, Fragility and Aging, Department of Biological Sciences, Faculty of Life Sciences, Universidad Andres Bello, Santiago, Chile; [3]Millennium Institute on Immunology and Immunotherapy, Faculty of Life Sciences, Universidad Andres Bello, Santiago, Chile; [4]Center for Biomedical Research and Innovation (CiiB), Faculty of Medicine, Universidad de los Andes, Santiago, Chile; [5]Facultad de Ciencias de la Salud, Escuela de Kinesiología, Universidad Bernardo O Higgins, Santiago, Chile; [6]Exercise and Rehabilitation Sciences Institute, School of Physical Therapy, Faculty of Rehabilitation Sciences, Universidad Andrés Bello, Santiago, Chile; [7]Escuela de Química y Farmacia, Facultad de Medicina, Universidad Andres Bello, Santiago, Chile; [8]Exercise and Rehabilitation Sciences Institute, Postgraduate, Faculty of Rehabilitation Sciences, Universidad Andres Bello, Santiago, Chile.

Abstract

Metabolic dysfunction-associated steatotic liver disease (MASLD) is a condition characterized by altered liver function due to fatty accumulation, which can lead to liver inflammation and, in advanced stages, liver carcinoma. MASLD is closely linked to several metabolic alterations, such as obesity and insulin resistance, which directly affect skeletal muscles and contribute to the development of sarcopenia. Sarcopenia is the loss of muscle mass and strength, leading to decreased physical performance in severe stages. Skeletal muscles secrete molecules known as myokines under various conditions, such as exercise or diseases like MASLD. These myokines modulate communication between the skeletal muscle and other tissues. These myokines regulate muscle mass and, in pathological conditions, contribute to the development of sarcopenia. Emerging evidence highlights the crucial role of myokines in regulating skeletal muscle metabolism and function in MASLD. Myokines influence muscle metabolism, inflammation, and insulin sensitivity, offering potential therapeutic targets for managing muscle atrophy and sarcopenia in the context of MASLD. Understanding the interaction between myokines and skeletal muscle may lead to novel interventions to mitigate MASLD progression and sarcopenia. This review examines the mechanisms by which myokines regulate skeletal muscle metabolism and function in the context of MASLD.

Key Words: metabolic dysfunction-associated steatotic liver disease, sarcopenia, myokines.

Eur J Transl Myol 35 (3) 13365, 2025 doi: 10.4081/ejtm.2025.13365

Metabolic dysfunction-Associated Steatotic Liver Disease (MASLD) is a type of chronic liver disease that has a prevalence rate of 38% worldwide.[1] MASLD encompasses various liver disorders, ranging from a fat buildup in the liver (*i.e.*, fatty liver) to inflammation and liver damage, known as non-alcoholic steatohepatitis.[2] Genetic, environmental, and metabolic risk factors influence the development of MASLD.[3,4] Among these, metabolic disorders, including insulin resistance, obesity, metabolic syndrome, and type 2 diabetes mellitus, are prominent lifestyle-related risk factors.[5,6] This condition is characterized by excessive fat accumulation in hepatocytes, which triggers inflammation and oxidative stress. Over time, this process can lead to progressive liver damage, resulting in cirrhosis, liver failure, or even carcinoma.

In addition to its effects on the liver, inflammation and ox-

idative stress produced by hepatocytes associated with MASLD extend to other tissues, such as the endothelium, peripheral nerves, heart, and skeletal muscles.[7] Skeletal muscle plays a crucial role in glucose uptake and whole-body metabolism, as it accounts for approximately 50% of body mass. Due to Insulin Resistance (IR) observed in MASLD, decreased muscle protein synthesis results from impaired insulin-dependent signaling. Moreover, IR can increase protein degradation, reducing muscle mass.[8] This decline in muscle mass has been associated with muscle weakness and the development of sarcopenia, typical features of patients with MASLD.[9,10] Sarcopenia is a skeletal muscle syndrome characterized by decreased muscle strength, mass, and physical performance, which can be secondarily developed due to pathological conditions, such as MASLD.[11,12] Sarcopenia has also been described by increased degradation and/or decreased synthesis of sarcomeric proteins, mitochondrial dysfunction, and oxidative stress in skeletal muscle.[7,13,14]

Some studies suggest that in MASLD, sarcopenia has been associated with an increased inflammatory state, which results in the release of pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), as well as other soluble molecules into the bloodstream, such as bile acids and ammonia. In addition, reduced plasma levels of insulin-like growth factor 1 (IGF-1), an anabolic factor in skeletal muscle, have also been reported in MASLD.[15] These circulating molecules have been shown to modulate muscle mass loss and contribute to the development of sarcopenia.[10,11,16]

In recent years, it has been described that skeletal muscle communicates with other tissues and organs, including the liver, adipose tissue, brain, and bone, by secretion of soluble molecules known as myokines.[17] Myokines exert autocrine, paracrine, and endocrine actions to regulate metabolic processes such as glucose uptake, lipid oxidation, and energy production.[18] It has been shown that MASLD modulates myokine secretion, which regulates muscle mass and the development of sarcopenia.[19,21] This review outlines the main effects of MASLD on myokine secretion and its muscular and systemic consequences.

Myokines regulate the metabolism and functions of the skeletal muscle in MASLD

Recent studies emphasize the essential role of myokines in regulating skeletal muscle characteristics and function. Myokines impact muscle metabolism, inflammation, and insulin sensitivity, which are expected consequences of MASLD. By elucidating the relationship between myokines and skeletal muscle, novel therapeutic strategies for managing MASLD can be discovered. This review will discuss the evidence of the most reported myokines in the literature, which include Myostatin, IL-6, IGF-1, IL-15, Irisin, LIF, FGF21, and Myonectin.

Myostatin

Myostatin, also known as growth differentiation factor 8 (GDF8), is a myokine belonging to the transforming growth factor-beta (TGF-β) superfamily of cytokines.[22] This myokine is expressed in cardiac and adipose tissue but is most abundant in skeletal muscle.[23] Myostatin is a negative regulator of muscle mass, and its absence increases muscle mass, contributing to hypertrophy.[24] Skeletal muscle cells synthesize pre-myostatin, which comprises an N-terminal pro-domain region, a biologically active C-terminal domain, and an N-terminal signal sequence. Proteolytic cleavage is required to activate it.[25] Myostatin acts on skeletal muscle to bind to the activin type II receptor B (ActRIIB), which activates the Smad signaling pathway, triggering the phosphorylation of Smad2/3 and forming a complex with Smad4.[23] This activated complex translocates into the nucleus, blocking the critical activity of myogenic regulator factors (MRF), including myoblast determination protein 1 (MyoD), myocyte-specific enhancer factor (MEF2), Myogenic factor 5 (Myf5), and myogenin.[26] This blockage halts the myoblast proliferation and differentiation, leading to the failure of the myogenic process. Also, myostatin activates the Forkhead box protein O1 (FoxO1), a transcriptional factor involved in the activation of protein degradation pathways, such as the Ubiquitin-Proteasome System (UPS), by increasing the expression of the E3-ligases MuRF-1 and atrogin-1.[27] On the other hand, myostatin inhibits muscle hypertrophy by downregulating the activity of the Akt/mTOR pathway, which is involved in protein synthesis.[23,25,28]

Under physiological conditions, myostatin is present in low concentrations in the bloodstream and skeletal muscle. However, chronic diseases (such as cancer), inflammatory conditions, sarcopenia, immobilization, bed rest, and traumatic musculoskeletal injury increase myostatin levels in muscle and serum.[2] Interestingly, myostatin expression decreases after acute and chronic endurance and resistance exercises in rodents and humans (compared to most myokines described to date).[29,30]

Regarding MASLD, the serum levels of myostatin are increased due to hyperammonemia developed in the late stage of the disease.31 This increment of myostatin is mediated by skeletal muscle through an NF-κB-dependent mechanism.[31-33] The elevated levels of myostatin induced by hyperammonemia decrease muscle mass due to the activation of the degradation mechanisms such as UPS and autophagy, which depend on NF-κB and FoxO.[26,34,35] The increase of myostatin in metabolic diseases has also been correlated with IR due to the downregulated expression of GLUT4 and the decreased phosphorylation of IRS1.[36] In the same direction, the absence of myostatin in KO mice improves IR and increases muscle mass in liver diseases.[37] Several strategies have been developed to inhibit myostatin expression or block its activity, improving muscle mass and metabolic functions in animal models.[38] Thus, blocking antibodies for myostatin or its receptors ActIIB or ActIIA have beneficial effects for treating muscle weakness in different diseases such as Duchenne muscular dystrophy (in the *mdx* model) or sarcopenia derived from chronic kidney disease or cancer, among others.[39-41] Specifically, follistatin, a soluble inhibitor of myostatin that competes for the binding to ActRIIA, which is in-

creased during exercise, positively affects muscle mass, inducing hypertrophy.[42-44]
In summary, increased myostatin levels observed under pathological conditions such as MASLD contribute to muscle wasting and sarcopenia (Figure 1), highlighting its potential as a therapeutic target for muscle-related disorders.

Interleukin 6 (IL-6)

IL-6 is a pro-inflammatory cytokine synthesized by several cell types, including activated monocytes/macrophages, vascular endothelial cells, fibroblasts, and skeletal muscle. It is crucial in triggering the acute phase reaction in the inflammatory process.[28] Under physiological conditions, circulating IL-6 levels are low but can increase more than 1,000-fold during an inflammatory state.[45] Beyond its role in inflammation, IL-6 is also crucial in metabolism by controlling body weight, liver physiology, and bone metabolism.[45] Within skeletal muscle, IL-6 can exhibit both pro-inflammatory and anti-inflammatory properties depending on the context. The pro-inflammatory actions of IL-6 are particularly evident during chronic inflammation, such as a response to an injury (*i.e.*, muscle damage).[46] Under these circumstances, elevated levels of TNF-α and IL-1β further amplify IL-6 production, which inhibits insulin activity, promotes IR, and could be a predictor for type 2 diabetes mellitus.[47] This pro-inflammatory function occurs through an increase in STAT3 activation, inhibiting PI3K-akt signaling, decreasing protein synthesis, and increasing myostatin expression, thereby contributing to the development of sarcopenia.[45,48]
The anti-inflammatory role of IL-6 is observed in response

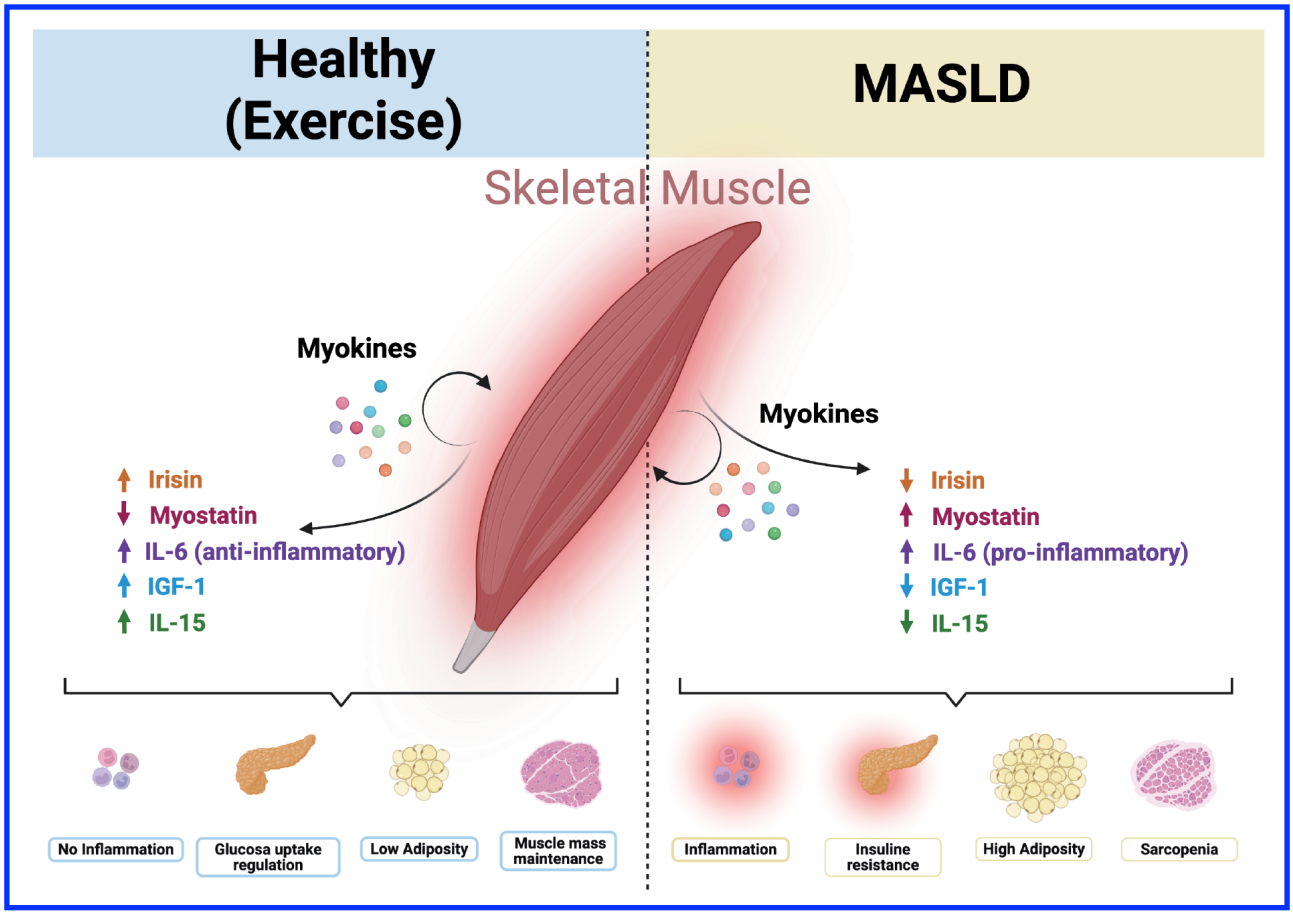

Figure 1. *Actions of myokines in healthy and pathological (MASLD) conditions. In MASLD, skeletal muscle releases myokines that promote liver dysfunction by altering glucose and lipid metabolism. These events produce insulin resistance and sarcopenia in the SM by increasing myostatin and IL-6 levels. Meanwhile, other myokines decrease their secretion in this condition, reinforcing sarcopenia and the metabolic disorders in skeletal muscle and liver (decreased irisin, IGF-1, and IL-15 levels). In healthy subjects, the exercise causes the release of myokines from the skeletal muscle producing an anti-inflammatory effect (increased IL-6 levels), metabolic control of glucose, insulin, and triglyceride levels, and muscle hypertrophy (increased irisin, IGF-1 and IL-15, and decreased myostatin levels).*
MASLD, metabolic dysfunction-associated steatotic liver disease; SM, skeletal muscle; IL, interleukin; IGF-1, insulin-like growth factor-1.

to muscle contraction in the absence of muscle injury.[49] During and following exercise, an acute increase in IL-6 is observed as a direct response to muscle contraction.[21,50] The peak concentration of IL-6 depends on the intensity of the exercise. During exercise, IL-6 positively affects various organs and tissues, improving glucose sensitivity and optimizing metabolism to provide energy substrates for muscle contraction.[51,52] IL-6 mediates its effects through interaction with its primary receptor (IL6Rα) and a secondary receptor (gp130), which activates several signaling pathways, including ERK1/2 MAPK, PI3K, Akt, and AMPK. This activation promotes increased glucose uptake and fatty acid oxidation.[46,50]

In MASLD patients, the severity of the condition is directly proportional to the increase in IL-6 levels.[53] Moreover, elevated IL-6 levels in MASLD are related to adverse effects, such as enhanced liver susceptibility to injury, inflammation, and even increased risk of liver cancer.[54] IL-6 activates STAT3, a lipogenic factor in hepatocytes, leading to hepatic steatosis in MASLD.[55] This, in turn, exacerbates NF-κB activity, which is also stimulated by IL-6. Elevated IL-6 levels mediate inflammation by recruiting Kupffer cells and contribute to IR through up-regulation of the suppressor cytokine signaling 3 (SOCS3).[56] In muscle tissue, IL-6 plays a pivotal role in IR and contributes to systemic low-grade inflammation, thereby aggravating the metabolic disorders associated with the disease.[45,52]

Thus, in chronic conditions such as MASLD, persistently elevated levels of IL-6 in the bloodstream increase the activity of catabolic pathways while decreasing anabolic pathways in skeletal muscle, thereby promoting the development of sarcopenia (Figure 1).

Insulin-like growth factor-1 (IGF-1)

IGF-1 is a growth factor that is also considered myokine. It consists of a single-chain polypeptide of 70 amino acids, cross-linked by three disulfide bridges, with a molecular weight of 7 kDa.[57] IGF-1 is mainly synthesized and secreted by the liver and skeletal muscles, exerting its functions on various target tissues in an endocrine, paracrine, and autocrine manner. Endurance and resistance training can increase IGF-1 levels in skeletal muscles, promoting cell growth and differentiation by stimulating anabolic pathways and decreasing catabolic pathways activity.[57,58] Specifically, IGF-1 binds to the IGF-1 receptor (IGF-1R), activates it by phosphorylation, and leads to activation of the AMPK/ERK and Akt/mTOR axes. This activation increases muscle protein synthesis and is expected to increase muscle mass.[59]

Patients with MASLD exhibit low serum levels of IGF-1 due to the severity of inflammation, hepatocyte ballooning, and liver fibrosis.[60,61] Under normal conditions, IGF-1 helps prevent IR, mitochondrial dysfunction, triglyceride accumulation, inflammation, and oxidative stress.[62] Consequently, reduced IGF-1 levels in NALD patients may exacerbate these events, activating hepatic stellate cells to produce more Extracellular Matrix (ECM) and leading to fibrogenesis and cirrhosis.[63]

In MASLD-induced sarcopenia, there is a direct correlation between reduced muscle mass and strength and decreased circulating IGF-1 levels.[16] This indicates that a decline in IGF-1 secretion could contribute to the development of sarcopenia in MASLD. Similarly, patients with obesity, often associated with fatty liver and MASLD, present a decreased expression of IGF-1 in skeletal muscle, leading to an imbalance in the IGF-1 axis and an increased risk of developing sarcopenia.[64] Interestingly, it should be noted that in cases of chronic liver disease, treatment with lithocholic acid has been shown to enhance IGF-1 signaling, improving protein synthesis and muscle mass.[65]

Thus, IGF-1 is a myokine associated with increased muscle mass and is secreted by skeletal muscle in response to exercise. A dysregulated IGF-1 axis can disrupt muscle mass regulation by increasing protein catabolism and reducing the activity of anabolism pathways, thereby inducing sarcopenia. In MASLD, the IGF-1 levels are low, which could contribute to the development of sarcopenia, a common symptom of liver disease (Figure 1).

Interleukin-15 (IL-15)

IL-15 is a 14 kDa myokine expressed and secreted in several non-lymphoid tissues, including the heart, lungs, and brain. In skeletal muscle, IL-15 is secreted in response to endurance or resistance exercise, depending more on the duration and intensity of the training than on its type.[66,67] IL-15 interacts with the IL-15 receptor alpha (IL-15Rα) and enhances the activity of peroxisome proliferator-activated receptor gamma (PPAR-g) and transcriptional co-activator peroxisome proliferator-activated receptor-gamma co-activator 1-alpha (PGC-1α), promoting anabolic processes in skeletal muscle, mainly related to hypertrophy, energy production, and mitochondrial biogenesis.[21,37,67,68] IL-15 also increases fatty acid oxidation, thermogenesis, and myogenesis, and promotes glucose uptake by activating the JAK3/STAT3 signaling pathway, which upregulates the gene expression of GLUT4 and its translocation to the sarcolemma.[69,70]

Individuals with metabolic diseases, such as obesity and type 2 diabetes mellitus, conditions associated with MASLD, exhibit lower expression and secretion of muscular IL-15. This reduction is related to an increased risk of developing sarcopenia.[66] Increased circulating levels of IL-15 have been observed to improve insulin resistance in women, a typical metabolic feature in MASLD.[71,72] In addition, increased expression and secretion of IL-15 from skeletal muscle into the circulation can lead to decreased body fat and inhibition of adiposity in obese mice.[73] This reduction in fat mass results from a decline in free fatty acid deposits in adipose tissue, inducing the input of energetic substrates to skeletal muscle.[69,74]

As mentioned above, IL-15 is a myokine mainly secreted by skeletal muscle in response to exercise, promoting muscle hypertrophy, energy production, and overall metabolic health. However, whether IL-15 can improve muscle function by enhancing energetic, metabolic, or anabolic processes in MASLD remains unknown. Further research is needed to determine whether IL-15 can be a potential therapeutic agent for improving muscle function and metabolic outcomes in patients with MASLD (Figure 1).

Irisin

Irisin is a 12 kDa myokine primarily synthesized and secreted by skeletal muscle, with smaller quantities produced in the liver and adipose tissue.[75,76] While irisin is known to target white adipocytes, myocytes, and hepatocytes,[77] its specific receptor has yet to be identified. Irisin expression is regulated by several factors, among them exercise, which increases its expression and secretion by a mechanism that depends on PGC-1α.[75,78] This mechanism involves the production of fibronectin type III domain-containing protein 5 (FNDC), a membrane protein that undergoes proteolytic cleavage to form irisin.[79] The overall steps to increase irisin expression by exercise are i) upregulation of PPAR-γ, a coactivator of PGC-1α in skeletal muscle, ii) subsequent elevation of FNDC5 expression driven by increased PGC-1α levels, iii) the generation of irisin via proteolytic cleavage of FNDC5 at the cell membrane through a proteolytic enzyme yet unknown.[17,80]

The expression and secretion of Irisin from skeletal muscles have been debated in recent years due to inconsistencies in results regarding the levels of this myokine in response to exercise. These discrepancies are often attributed to variations in detection methods (e.g., ELISA, commercial kits), highlighting the need for more rigorous evaluation to clarify and understand the regulation of irisin through exercise.[81-84]

Functionally, Irisin induces myogenesis and mitochondrial biogenesis in skeletal muscle, offering protection against sarcopenia.[80,85] Irisin elevates protein anabolism by increasing IGF-1 production and activating protein synthesis-associated signaling pathways (phosphoinositide 3-kinase (PI3K)/protein kinase B (33), mTOR). This effect favors muscle hypertrophy and activation of progenitor stem cells in skeletal muscle (satellite cells). In addition, irisin reduces the activity of protein catabolic pathways (e.g., a reduction in the levels of atrogin-1 and MuRF-1)[80,84] and may inhibit the expression of catabolic myokines, such as myostatin. Thus, the antecedents support the idea that an experimental approach using exogenous irisin could be a helpful strategy in the management of sarcopenia.[86] Interestingly, a transition of high levels of irisin to a significantly lower level will predict the development of sarcopenia in MASLD.[87]

Irisin also affects tissues beyond skeletal muscle, particularly adipose tissue, enhancing thermogenesis and energy expenditure.[88] Moreover, Irisin causes changes in adipose tissue, reducing white adipose tissue and increasing Brown Adipose Tissue (BAT), such as gene expression, morphology, and mitochondrial activity. This mechanism and thermogenesis depend on PGC-1α dependent increased expression of UCP1.[89]

Irisin also affects the liver, regulating glucose and lipid metabolism by reducing gluconeogenesis and promoting glycogenesis, thus improving glucose homeostasis via activation of PI3K/Akt[33] and AMPK pathways.[90,91] Regarding lipid metabolism, irisin prevents lipid accumulation by enhancing lipolysis in hepatocytes and lowering cholesterol and triglyceride levels through AMPK activation and subsequent inhibition of sterol regulatory element-binding transcription factor 2 (SREBP2), a key regulator of cholesterol homeostasis.[92] Despite evidence suggesting that serum irisin levels are elevated in patients with MASLD, correlating with its severity,[93,94] caution must be considered due to the small sample size, leading to results that must be clarified.[84]

Despite these uncertainties, Irisin holds potential as a therapeutic target in treating complications associated with obesity, including MASLD, although the mechanisms underlying these benefits remain to be fully elucidated. Future research should focus on clarifying the role of irisin in alterations observed in MASLD, such as hepatic oxidative stress and apoptosis, and its role in hepatocellular carcinoma.[17]

In summary, irisin is a myokine with beneficial effects on adipose tissue, liver, and skeletal muscle. In MASLD, elevated irisin levels are associated with abnormal body composition, insulin resistance, glucose metabolism, plasma lipid levels, and liver enzyme activity (Figure 1).

Other myokines related to MASLD

Several new myokines have been studied for their potential roles in MASLD in recent years.

Leukemia inhibitory factor (LIF)

Leukemia inhibitory factor (LIF) is a 20 kDa myokine secreted by neurons, cardiac and skeletal muscle. Its expression increases in skeletal muscle, but not in serum, after resistance exercise, stimulating satellite cell proliferation.[95,96] Additionally, LIF production and secretion have been observed in human myotube cell cultures following electrical stimulation, suggesting that LIF is a myokine with an autocrine effect on skeletal muscle.[97]

In MASLD, serum LIF levels are associated with the severity of hepatic in patients with liver damage and a murine model of obesity.[98] Patients with liver fibrosis, lobar inflammation, and increased serum levels of Alanine Transaminase (ALT) and aspartate Aminotransferase (AST) (two hepatic enzymes related to liver damage) showed an increase in levels of LIF.[91] Interestingly, overexpression of LIF in adipose tissue produces a protective function in an MASLD condition, reducing the inflammatory state by reducing the expression of pro-inflammatory cytokines such as tnf-α, il6, and *ccl2*. In addition, under these conditions, an improvement in fatty tissue metabolism, glucose tolerance, and insulin sensitivity has been observed. The same beneficial effects were observed in the liver when the LIF receptor (LIFR) was overexpressed in a murine model of obesity, indicating that the LIF receptor has a protective role in the liver.[98,99] However, further studies are needed to clarify the function of LIF in skeletal muscle in MASLD (Figure 1).

Fibroblast growth factors 21 (FGF21)

FGF21 is a molecule expressed by various tissues, including the liver, adipose tissue, and skeletal muscle, in response to different stress states, such as cold exposure, fasting, and exercise. FGF21 acts through the FGF receptor (FGFR) and the cofactor β-klotho.[96] During resistance exercise, FGF21 expression increases in skeletal muscle,

contributing to converting slow-twitch fibers muscle to fast-twitch fibers in the gastrocnemius muscle of mice. In addition, FGF21 decreases TGF-β1 signaling and increases MAPK p38 signaling in muscle cells, increasing glucose uptake and reducing lipid accumulation in the muscle.[100,101] However, it has also been reported that FGF21 is increased in skeletal muscle in steatosis conditions.[102] In FGF21 KO mice was observed a protective effect on muscle mass loss during starvation, supporting the idea that FGF21 could be an anti-sarcopenic soluble factor by preventing decreased protein synthesis and altered mitophagy.[103,104]

Regarding MASLD, FGF21 reduces triglyceride accumulation in hepatocytes (steatosis) due to lipolysis inhibition, decreasing the concentration of fatty acids in the circulation and reducing their accumulation in the liver.[105] FGF21 also decreases plasma glucose in ob/ob mouse models and mitigates hepatic oxidative stress by activating the FGFR/AMPK/Sirt1 signaling pathway, which upregulates antioxidant enzymes such as Nrf2 and SOD.[106,107] Moreover, FGF21 has been shown to reduce hepatic inflammation in MASLD by activating the Nrf2 pathway and inhibiting NF-κB signaling.[108]

In summary, FGF21 is a myokine regulated in skeletal muscle by exercise, with its role in muscle mass regulation depending on the stimulus and the physiological context. It can participate in muscle mass gain through inhibiting TGF-β1 and is associated with the development of sarcopenia due to starvation. Concerning MASLD, circulating levels of FGF21 are elevated and directly correlate with the severity of liver damage and steatosis (Figure 1).

Myonectin

Myonectin is a myokine secreted in response to exercise and belongs to the C1q/TNF (CTRP) protein family.[109] This myokine participates in the absorption of fatty acids through the increase in the expression of Fatty Acid Transporters (FATP1) and fatty acid binding proteins (Fabp1 and Fabp4).[73] Myonectin also reduces starvation-induced autophagy by decreasing the formation of LC3-dependent autophagosomes and p62.[110] Additionally, myonectin has been described as a potentiator of protein synthesis through the PI3K/Akt/mTOR signaling pathway, indicating that this myokine can positively regulate muscle mass by increasing protein synthesis and decreasing the degradation process, specifically autophagy. Some studies have associated myonectin with a protective role in skeletal muscle through AMPK/PGC1a signaling, attenuating sarcopenia induced by denervation and dexamethasone.[20,73,111]

In MASLD, various metabolic disorders, such as diabetes mellitus, have been associated with levels of myonectin. For instance, in patients with type 2 diabetes mellitus and obesity, the concentration of myonectin in the serum has been negatively associated with an increase in circulating triglycerides, LDL, and total cholesterol,[112,113] which may reflect a state of resistance to myonectin. Interestingly, moderate and high-intensity exercise can increase the serum levels of myonectin in MASLD patients, indicating a possible improvement in lipid metabolism by exercise-induced elevations in circulating myonectin.[114-116]

To summarize, myonectin is a myokine whose expression is regulated by exercise and is protective against muscle mass loss in sarcopenia conditions. However, more research is still needed to understand its association with MASLD and its molecular roles in skeletal muscle and the liver (Figure 1).

Conclusions and perspectives

Skeletal muscle releases myokines under physiological and pathological conditions. Some myokines are released at rest, while others are secreted during or after muscle contraction (e.g., exercise). These myokines can function in an autocrine, paracrine, or endocrine manner in various tissues and organs, such as the liver and adipose tissue. Some well-known myokines include irisin, myostatin, IL-6, IL-15, IGF-1, LIF, FGF21, and myonectin.

Some myokines are produced and secreted during exercise in response to muscle contraction. They perform essential functions such as increasing muscle mass, protecting against muscle degradation, and promoting energy metabolism and glucose homeostasis.

Myokines have shown detrimental effects in pathological conditions, including MASLD. For instance, irisin can affect body composition, while myostatin, IL-6, and irisin can affect insulin and glucose homeostasis. IL-6 is associated with liver injury and chronic inflammation, while myostatin, IGF-1, and IL-6 affect skeletal muscle mass. Some myokines, such as LIF and FGF21, are related to the severity of MASLD (*i.e.*, increased steatosis or increased circulating triglycerides).

The precise roles of myokines in MASLD must still be fully understood. Future research must include well-controlled clinical studies to determine their functions and biochemical mechanisms of action in humans. Myokines have the potential to be new targets for preventing or treating sarcopenia in metabolic diseases like MASLD.

List of abbreviations

FGF21, Fibroblast growth factors 21
GDF8, Growth differentiation factor 8
IGF-1, Insulin-like growth factor 1
IL-6, Interleukin-6
IL-15, Interleukin-15
IR, Insulin resistance
LIF, Leukemia inhibitory factor
MASLD,: Metabolic dysfunction-associated steatotic liver disease
MAFbx1/atrogin-1, Muscle-specific F-box protein 1
MuRF-1, Muscle RING-finger protein1
PI3K, Phosphoinositide 3-kinase /protein kinase B
TGF-β, Transforming growth factor-beta
TNF-α, Tumor necrosis factor-alpha
UPS, Ubiquitin-proteasome system

Funding

The manuscript was supported by research grants from the National Fund for Science and Technological Devel-

opment (FONDECYT 1241947 [C.C-V.], 1211879 [D.C.], 1211962 [L.P.]); Agencia Nacional de Investigación y Desarrollo (ANID)-Millennium Science Initiative Program - ICN09_016 / ICN 2021_045: Millennium Institute on Immunology and Immunotherapy (ICN09_016 / ICN 2021_045; former P09/016-F) [C.C-V.]). Proyecto Núcleo UNAB (DI-03-23/NUC [C.C-V.]; DI-02-22/NUC [C.O.]). Beca Doctorado Nacional ANID (21212005 [M.V-B.], 21201447 [F.A.]). Beca VRI UNAB N° DI-05-21/INI [M.V-B.].

Conflict of interest

The authors declare that they have no conflict of interest.

Ethical approval

All animal procedures complied with international, national, and institutional animal care guidelines and were approved by the Animal Ethics Committee at the Universidad Andrés Bello Committee.

Author contributions

Conceptualization, FA, and CC-V; Methodology, FA, MV-B, and CC-V; Validation, FA, MV-B, DC, LP, CO, and CC-V; Investigation, FA, M V-B, DC and CC-V; Visualization, FA, MV-B, CO, and CC-V; Supervision CC-V; Project administration, CC-V; Writing – Original Draft Preparation, FA, MV-B, DC LP, CO, CF, and CC-V; Writing – Review & Editing, FA, MV-B, DC, CF, LP, CO, and CC-V

Corresponding author

Claudio Cabello-Verrugio, Center for Research on Pandemic Resilience, Faculty of Life Sciences and Institute of Public Health, Universidad Andres Bello. Santiago, 8370146, Chile.
Tel./Fax: +56.2.27703665.
ORCID ID: 0000-0001-7273-2102
E-mail: claudio.cabello@unab.cl

Co-authors

Francisco Aguirre
ORCID ID: 0000-0001-8103-9473
E-mail: f.aguirregalaz@uandresbello.edu

Mayalen Valero-Breton
ORCID ID: 0000-0001-6552-2262
E-mail: m.valerobreton@uandresbello.edu

Daniel Cabrera
ORCID ID: 0000-0001-9634-725X
E-mail: dacabrera@uandes.cl

Luis Peñailillo
ORCID ID: 0000-0001-7697-9700
E-mail: luis.penailillo@unab.cl

Carolina Otero
ORCID ID: 0000-0002-8608-9813
E-mail: maría.otero@unab.cl

Claudia Fredes
ORCID ID: 0000-0002-5526-1801
E-mail: claudia.fredes@unab.cl

References

1. Teng ML, Ng CH, Huang DQ, et al. Global incidence and prevalence of nonalcoholic fatty liver disease. Clin Mol Hepatol 2023;29:S32-s42.
2. Klionsky DJ, Abdel-Aziz AK, Abdelfatah S, et al. Guidelines for the use and interpretation of assays for monitoring autophagy (4th edition)(1). Autophagy 2021;17:1-382.
3. Zarghamravanbakhsh P, Frenkel M, Poretsky L. Metabolic causes and consequences of nonalcoholic fatty liver disease (NAFLD). Metabol Open 2021;12: 100149.
4. Younossi ZM. Nonalcoholic fatty liver disease and nonalcoholic steatohepatitis: Implications for liver transplantation. Liver Transpl 2018;24:166-70.
5. Yeo Y-H, Lai Y-C. Redox regulation of metabolic syndrome: recent developments in skeletal muscle insulin resistance and non-alcoholic fatty liver disease (NAFLD). Curr Opin Physiol 2019;9:79-86.
6. Forlani G, Giorda C, Manti R, et al. The Burden of NAFLD and Its Characteristics in a Nationwide Population with Type 2 Diabetes. J Diabetes Res 2016;2 016:2931985.
7. Gonzalez A, Huerta-Salgado C, Orozco-Aguilar J, et al. Role of oxidative stress in hepatic and extrahepatic dysfunctions during nonalcoholic fatty liver disease (NAFLD). Oxid Med Cell Longev 2020;2020:1617805.
8. Feraco A, Gorini S, Armani A, et al. Exploring the role of skeletal muscle in insulin resistance: lessons from cultured cells to animal models. Int J Mol Sci 2021;22: 9327.
9. Su X, Xu J, Zheng C. The relationship between non-alcoholic fatty liver and skeletal muscle mass to visceral fat area ratio in women with type 2 diabetes. BMC Endocr Disord 2019;19:76.
10. Pacifico L, Perla FM, Chiesa C. Sarcopenia and non-alcoholic fatty liver disease: a causal relationship. Hepatobiliary Surg Nutr 2019;8:144-7.
11. Fernandez-Mincone T, Contreras-Briceno F, Espinosa-Ramirez M, et al. Non-alcoholic fatty liver disease and sarcopenia: pathophysiological connections and therapeutic implications. Expert Rev Gastroenterol Hepatol 2020;14:1141-1157.
12. Cruz-Jentoft AJ, Bahat G, Bauer J, et al. Sarcopenia: revised European consensus on definition and diagnosis. Age Ageing 2019;48:16-31.
13. Campos F, Abrigo J, Aguirre F, et al. Sarcopenia in a mice model of chronic liver disease: role of the ubiquitin–proteasome system and oxidative stress. Pflügers Archiv - Eur J Physiol 2018;470:1503-19. d
14. Aguirre F, Abrigo J, Gonzalez F, et al. Protective Effect

of Angiotensin 1-7 on Sarcopenia Induced by Chronic Liver Disease in Mice. Int J Mol Sci 2020;21:3891.
15. Takahashi Y. Nonalcoholic fatty liver disease and adult growth hormone deficiency: An under-recognized association? Best Practice Res Clin Endocrinol Metab 2023;37:101816.
16. Cabrera D, Ruiz A, Cabello-Verrugio C, et al. Diet-induced nonalcoholic fatty liver disease is associated with sarcopenia and decreased serum insulin-like growth factor-1. Dig Dis Sci 2016;61:3190-8.
17. Polyzos SA, Anastasilakis AD, Efstathiadou ZA, et al. Irisin in metabolic diseases. Endocrine 2018;59:260-74.
18. Chen Z-T, Weng Z-X, Lin JD, Meng Z-X. Myokines: metabolic regulation in obesity and type 2 diabetes. Life Metabolism 2024;3:loae006.
19. Cai C, Song X, Chen Y, Chen X, Yu C. Relationship between relative skeletal muscle mass and nonalcoholic fatty liver disease: a systematic review and meta-analysis. Hepatol Int 2020;14:115-26.
20. Lee JH, Jun H-S. Role of myokines in regulating skeletal muscle mass and function. Front Physiol 2019;10:42.
21. Gomarasca M, Banfi G, Lombardi G. Myokines: The endocrine coupling of skeletal muscle and bone. Adv Clin Chem 2020;94:155–218.
22. Baczek J, Silkiewicz M, Wojszel ZB. Myostatin as a biomarker of muscle wasting and other pathologies-state of the art and knowledge gaps. Nutrients 2020;12:2401.
23. Chen M-M, Zhao Y-P, Zhao Y, et al. Regulation of myostatin on the growth and development of skeletal muscle. Front Cell Dev Biol 2021;9:785712.
24. Morvan F, Rondeau J-M, Zou C, et al. Blockade of activin type II receptors with a dual anti-ActRIIA/IIB antibody is critical to promote maximal skeletal muscle hypertrophy. Proc Nat Acad Sci 2017;114:12448.
25. Omosule CL, Phillips CL. Deciphering myostatin's regulatory, metabolic, and developmental influence in skeletal diseases. Front Genet 2021;12:662908.
26. Sartori R, Romanello V, Sandri M. Mechanisms of muscle atrophy and hypertrophy: implications in health and disease. Nat Commun 2021;12:330.
27. Hildebrandt L, Dieterlen MT, Klaeske K, et al. Myostatin/AKT/FOXO Signaling Is Altered in Human Non-Ischemic Dilated Cardiomyopathy. Life (Basel) 2022;12:1418.
28. Gomarasca M, Banfi G, Lombardi G. Myokines: The endocrine coupling of skeletal muscle and bone. Adv Clin Chem 2020;94:155-218.
29. Piccirillo R. Exercise-induced myokines with therapeutic potential for muscle wasting. Front Physiol 2019;10:287.
30. Zhou Y, Hellberg M, Hellmark T, Höglund P, Clyne N. Muscle mass and plasma myostatin after exercise training: a substudy of Renal Exercise (RENEXC)—a randomized controlled trial. Nephrol Dial Transplant 2019;36:95-103.
31. Stern RA, Dasarathy S, Mozdziak PE. Ammonia Induces a myostatin-mediated atrophy in mammalian myotubes, but induces hypertrophy in avian myotubes. Front Sustainable Food Systems 2019;3:115.
32. Qiu J, Tsien C, Thapalaya S, et al. Hyperammonemia-mediated autophagy in skeletal muscle contributes to sarcopenia of cirrhosis. Am J Physiol Endocrinol Metab 2012;303:E983-93.
33. Ruiz-Margáin A, Pohlmann A, Lanzerath S, et al. Myostatin is associated with the presence and development of acute-on-chronic liver failure. JHEP Reports 2023;5:100761.
34. Davuluri G, Allawy A, Thapaliya S, et al. Hyperammonaemia-induced skeletal muscle mitochondrial dysfunction results in cataplerosis and oxidative stress. J Physiol 2016;594:7341-60.
35. Aravena J, Abrigo J, Gonzalez F, et al. Angiotensin (1-7) Decreases Myostatin-Induced NF-kappaB Signaling and Skeletal Muscle Atrophy. Int J Mol Sci 2020;21:1167.
36. Amor M, Itariu BK, Moreno-Viedma V, et al. Serum myostatin is upregulated in obesity and correlates with insulin resistance in humans. Exp Clin Endocrinol Diabetes 2019;127:550-6.
37. Gonzalez-Gil AM, Elizondo-Montemayor L. The role of exercise in the interplay between myokines, hepatokines, osteokines, adipokines, and modulation of inflammation for energy substrate redistribution and fat mass loss: a review. Nutrients 2020;12:1899.
38. Jang J, Park S, Kim Y, et al. Myostatin inhibition-induced increase in muscle mass and strength was amplified by resistance exercise training, and dietary essential amino acids improved muscle quality in mice. Nutrients 2021;13:1508.
39. Shi C, Zijlstra SN, Wit SD, et al. Divergent effects of myostatin inhibition on cardiac and skeletal muscles in a mouse model of pressure overload. Am J Physiol - Heart Circ Physiol 2023;325:H195-H201.
40. Rybalka E, Timpani CA, Debruin DA, et al. The failed clinical story of myostatin inhibitors against duchenne muscular dystrophy: exploring the biology behind the battle. Cells 2020;9:2657.
41. Breitbart A, Auger-Messier M, Molkentin JD, Heineke J. Myostatin from the Heart—Local and Systemic Actions in Cardiac Failure and Muscle Wasting. Am J Physiol Heart Circ Physiol 2011;300:H1973-82
42. Wallner C, Jaurich H, Wagner JM, et al. Inhibition of GDF8 (Myostatin) accelerates bone regeneration in diabetes mellitus type 2. Sci Rep 2017;7:9878.
43. Moore U, Fernández-Simón E, Schiava M, et al. Myostatin and follistatin as monitoring and prognostic biomarkers in dysferlinopathy. Neuromusc Dis 2023;33:199-207.
44. Fife E, Kostka J, Kroc Ł, et al. Relationship of muscle function to circulating myostatin, follistatin and GDF11 in older women and men. BMC Geriatrics 2018;18:200.
45. Rose-John S. Interleukin-6 signalling in health and disease. F1000Res. 2020;9:8.1.
46. Lin W, Song H, Shen J, et al. Functional role of skeletal muscle-derived interleukin-6 and its effects on lipid metabolism. Front Physiol 2023;14:1110926.
47. Nelke C, Dziewas R, Minnerup J, et al. Skeletal muscle as potential central link between sarcopenia and immune senescence. eBioMedicine 2019;49:381-8.

48. Shen Y, Li M, Wang K, et al. Diabetic muscular atrophy: molecular mechanisms and promising therapies. Front Endocrinol 2022;13:917113.
49. Nash D, Hughes MG, Butcher L, et al. IL-6 signaling in acute exercise and chronic training: Potential consequences for health and athletic performance. Scand J Med Sci Sports 2023;33:4-19.
50. Kistner TM, Pedersen BK, Lieberman DE. Interleukin 6 as an energy allocator in muscle tissue. Nature Metabolism 2022;4:170-9.
51. Rogeri PS, Gasparini SO, Martins GL, et al. Crosstalk between skeletal muscle and immune system: which roles do IL-6 and glutamine play? Front Physiol 2020; 11:582258.
52. Lombardi G, Sanchis-Gomar F, Perego S, et al. Implications of exercise-induced adipo-myokines in bone metabolism. Endocrine 2016;54:284-305.
53. Wieckowska A, Papouchado BG, Li Z, et al. Increased hepatic and circulating interleukin-6 levels in human nonalcoholic steatohepatitis. Am J Gastroenterol 2008;103:1372-9.
54. Duan Y, Pan X, Luo J, et al. Association of inflammatory cytokines with non-alcoholic fatty liver disease. Front Immunol 2022;13:880298.
55. Belloni L, Di Cocco S, Guerrieri F, et al. Targeting a phospho-STAT3-miRNAs pathway improves vesicular hepatic steatosis in an in vitro and in vivo model. Sci Rep 2018;8:13638.
56. Cobbina E, Akhlaghi F. Non-alcoholic fatty liver disease (NAFLD) - pathogenesis, classification, and effect on drug metabolizing enzymes and transporters. Drug Metab Rev 2017;49:197-211.
57. Mathes S, Fahrner A, Luca E, Krützfeldt J. Growth hormone/IGF-I-dependent signaling restores decreased expression of the myokine SPARC in aged skeletal muscle. J Mol Med (Berl) 2022;100:1647-58.
58. Scicchitano BM, Dobrowolny G, Sica G, Musaro A. Molecular insights into muscle homeostasis, atrophy and wasting. Curr Genomics 2018;19:356-69.
59. Yoshida T, Delafontaine P. Mechanisms of IGF-1-Mediated Regulation of Skeletal Muscle Hypertrophy and Atrophy. Cells 2020;9:1970.
60. Takahashi Y. The role of growth hormone and insulin-like growth factor-i in the liver. Int J Mol Sci 2017;18: 1447.
61. Dichtel LE, Corey KE, Misdraji J, et al. The association between IGF-1 levels and the histologic severity of nonalcoholic fatty liver disease. Clin Transl Gastroenterol 2017;8:e217.
62. Sádaba MC, Martín-Estal I, Puche JE, Castilla-Cortázar I. Insulin-like growth factor 1 (IGF-1) therapy: Mitochondrial dysfunction and diseases. Biochimica et Biophysica Acta (BBA) - Molec Basis Dis 2016;1862: 1267-78.
63. de la Garza RG, Morales-Garza LA, Martin-Estal I, Castilla-Cortazar I. Insulin-Like Growth Factor-1 Deficiency and Cirrhosis Establishment. J Clin Med Res 2017;9:233-47.
64. Sullivan EH, Gibson LE, Berra L, et al. In-hospital airway management of COVID-19 patients. Crit Care 2020;24:292.
65. Tamai Y, Eguchi A, Shigefuku R, et al. Association of lithocholic acid with skeletal muscle hypertrophy through TGR5-IGF-1 and skeletal muscle mass in cultured mouse myotubes, chronic liver disease rats and humans. eLife 2022;11:80638.
66. Nadeau L, Aguer C. Interleukin-15 as a myokine: mechanistic insight into its effect on skeletal muscle metabolism. Appl Physiol Nutr Metabolism 2019;44: 229-38. d
67. Pérez-López A, McKendry J, Martin-Rincon M, et al. Skeletal muscle IL-15/IL-15Rα and myofibrillar protein synthesis after resistance exercise. Scand J Med Sci Sports 2018;28:116-25.
68. Nadeau L, Patten DA, Caron A, et al. IL-15 improves skeletal muscle oxidative metabolism and glucose uptake in association with increased respiratory chain supercomplex formation and AMPK pathway activation. Biochim Biophys Acta Gen Subj 2019;1863:395-407.
69. Fujimoto T, Sugimoto K, Takahashi T, et al. Overexpression of Interleukin-15 exhibits improved glucose tolerance and promotes GLUT4 translocation via AMP-Activated protein kinase pathway in skeletal muscle. Biochem Biophys Res Comm 2019;509:994-1000.
70. Gomarasca M, Banfi G, Lombardi G. Chapter Four - Myokines: The endocrine coupling of skeletal muscle and bone. In: Makowski GS, editor. Adv Clin Chem 2020;94:155-218.
71. Orsatti CL, Orsatti FL, Bezerra TG, et al. Interleukin-15 are associated with insulin resistance in postmenopausal women with metabolic syndrome. Gynecol Endocrinol 2022;38:765-70.
72. Pistilli EE, Quinn LS. From anabolic to oxidative: reconsidering the roles of IL-15 and IL-15Rα in skeletal muscle. Exerc Sport Sci Rev 2013;41:100-6.
73. Dumond Bourie A, Potier JB, Pinget M, Bouzakri K. Myokines: crosstalk and consequences on liver physiopathology. Nutrients 2023;15:1729.
74. Sima AR, Sima HR, Rafatpanah H, et al. Serum chemokine ligand 5 (CCL5/RANTES) level might be utilized as a predictive marker of tumor behavior and disease prognosis in patients with gastric adenocarcinoma. J Gastrointest Cancer 2014;45:476-80.
75. Huh JY. The role of exercise-induced myokines in regulating metabolism. Arch Pharm Res 2018;41:14-29.
76. Waseem R, Shamsi A, Mohammad T, et al. FNDC5/Irisin: Physiology and Pathophysiology. Molecules 2022; 27:1118.
77. Zhao R. Irisin at the crossroads of inter-organ communications: Challenge and implications. Front Endocrinol (Lausanne) 2022;13:989135.
78. Norheim F, Langleite TM, Hjorth M, et al. The effects of acute and chronic exercise on PGC-1α, irisin and browning of subcutaneous adipose tissue in humans. Febs J 2014;281:739-49.
79. Jin Y, Sumsuzzman DM, Choi J, et al. Molecular and Functional interaction of the myokine irisin with physical exercise and Alzheimer's disease. Molecules 2018;23:3229.

80. Reza MM, Subramaniyam N, Sim CM, et al. Irisin is a pro-myogenic factor that induces skeletal muscle hypertrophy and rescues denervation-induced atrophy. Nat Commun 2017;8:1104.
81. Li H, Wang F, Yang M, et al. The effect of irisin as a metabolic regulator and its therapeutic potential for obesity. Int J Endocrinol 2021;2021:6572342.
82. Cosio PL, Crespo-Posadas M, Velarde-Sotres Á, Pelaez M. Effect of chronic resistance training on circulating irisin: systematic review and meta-analysis of randomized controlled trials. Int J Environ Res Public Health 2021;18:2476.
83. Amanat S, Sinaei E, Panji M, et al. A randomized controlled trial on the effects of 12 weeks of aerobic, resistance, and combined exercises training on the serum levels of Nesfatin-1, Irisin-1 and HOMA-IR. Front Physiol 2020;11:562895.
84. Ma C, Ding H, Deng Y, et al. Irisin: a new code uncover the relationship of skeletal muscle and cardiovascular health during exercise. Front Physiol 2021;12: 620608.
85. Zhao M, Zhou X, Yuan C, et al. Association between serum irisin concentrations and sarcopenia in patients with liver cirrhosis: a cross-sectional study. Sci Rep 2020;10:16093.
86. Alzoughool F, Al-Zghoul MB, Ghanim BY, et al. Impact of Sustained exogenous irisin myokine administration on muscle and myocyte integrity in sprague dawley rats. Metabolites 2022;12:939.
87. Al-Nimer MS. Interaction between inflammatory bowel disease, physical activity, and myokines: Assessment of serum irisin levels. World J Gastroenterol 2024;30: 2923-6.
88. Jin Y, Sumsuzzman DM, Choi J, et al. Molecular and Functional interaction of the myokine irisin with physical exercise and alzheimer's disease. Molecules 2018;23:3229.
89. Arhire LI, Mihalache L, Covasa M. Irisin: A hope in understanding and managing obesity and metabolic syndrome. Front Endocrinol (Lausanne) 2019;10:524.
90. Cui B, Fan X, Guo G, et al. The potential role of FNDC5/irisin in various liver diseases: awakening the sleeping beauties. Expert Rev Molec Med 2022; 24:e23.
91. Zhao J, Qiao L, Dong J, Wu R. Antioxidant effects of irisin in liver diseases: mechanistic insights. Oxid Med Cell Longev 2022;2022:3563518.
92. Tang H, Yu R, Liu S, et al. Irisin inhibits hepatic cholesterol synthesis via AMPK-SREBP2 signaling. EBioMedicine 2016;6:139-48.
93. Hu J, Ke Y, Wu F, et al. Circulating irisin levels in patients with nonalcoholic fatty liver disease: a systematic review and meta-analysis. Gastroenterol Res Pract 2020;2020:8818191.
94. Kosmalski M, Drzewoski J, Szymczak-Pajor I, et al. Irisin Is related to non-alcoholic fatty liver disease (NAFLD). Biomedicines 2022;10:2253.
95. Broholm C, Pedersen BK. Leukaemia inhibitory factor—an exercise-induced myokine. Exerc Immunol Rev 2010;16:77-85.
96. Lee HJ, Lee JO, Lee YW, et al. LIF, a Novel myokine, protects against amyloid-beta-induced neurotoxicity via akt-mediated autophagy signaling in hippocampal cells. Int J Neuropsychopharmacol 2019;22:402-14.
97. Broholm C, Laye MJ, Brandt C, et al. LIF is a contraction-induced myokine stimulating human myocyte proliferation. J Appl Physiol (1985) 2011;111:251-9.
98. Yuan Y, Li K, Teng F, et al. Leukemia inhibitory factor protects against liver steatosis in nonalcoholic fatty liver disease patients and obese mice. J Biol Chem 2022;298: 101946.
99. Guo T, Gupta A, Yu J, et al. LIFR-α-dependent adipocyte signaling in obesity limits adipose expansion contributing to fatty liver disease. iScience 2021;24: 102227.
100. Luo X, Zhang H, Cao X, et al. Endurance Exercise-Induced Fgf21 Promotes Skeletal Muscle Fiber Conversion through TGF-β1 and p38 MAPK Signaling Pathway. Int J Mol Sci 2023;24:11401.
101. Porflitt-Rodríguez M, Guzmán-Arriagada V, Sandoval-Valderrama R, et al. Effects of aerobic exercise on fibroblast growth factor 21 in overweight and obesity. A systematic review. Metabolism 2022;129:155137.
102. Tillman EJ, Rolph T. FGF21: an emerging therapeutic target for non-alcoholic steatohepatitis and related metabolic diseases. Front Endocrinol 2020;11:601290.
103. Oost LJ, Kustermann M, Armani A, et al. Fibroblast growth factor 21 controls mitophagy and muscle mass. J Cachexia Sarcopenia Muscle 2019;10:630-42.
104. Larson KR, Jayakrishnan D, Soto Sauza KA, et al. FGF21 induces skeletal muscle atrophy and increases amino acids in female mice: a potential role for glucocorticoids. Endocrinology 2024;165:4.
105. Li Z, Zhao B, Kim YS, et al. Administration of a mutated myostatin propeptide to neonatal mice significantly enhances skeletal muscle growth. Mol Reprod Dev 2010;77:76-82.
106. Zhang Y, Yin R, Lang J, et al. Epigallocatechin-3-gallate ameliorates hepatic damages by relieve FGF21 resistance and promotion of FGF21–AMPK pathway in mice fed a high fat diet. Diabetol Metabol Syndrome 2022;14:53.
107. Zhu S, Ma L, Wu Y, Ye X, Zhang T, Zhang Q, et al. FGF21 treatment ameliorates alcoholic fatty liver through activation of AMPK-SIRT1 pathway. Acta Biochimica et Biophysica Sinica. 2014;46(12):1041-8. doi: 10.1093/abbs/gmu097.
108. Wang Z, Sun T, Yu J, et al. FGF21: a sharp weapon in the process of exercise to improve NAFLD. FBL 2023;28:351.
109. Seldin MM, Peterson JM, Byerly MS, et al. Myonectin (CTRP15), a novel myokine that links skeletal muscle to systemic lipid homeostasis. J Biol Chem 2012;287:11968-80.
110. Seldin MM, Lei X, Tan SY, et al. Skeletal muscle-derived myonectin activates the mammalian target of rapamycin (mTOR) pathway to suppress autophagy in liver. J Biol Chem 2013;288:36073-82.
111. Ozaki Y, Ohashi K, Otaka N, et al. Myonectin protects against skeletal muscle dysfunction in male mice

through activation of AMPK/PGC1α pathway. Nat Commun 2023;14:4675.
112. Li Z, Yang YL, Zhu YJ, et al. Circulating serum myonectin levels in obesity and type 2 diabetes mellitus. Exp Clin Endocrinol Diabetes 2021;129:528-34.
113. Petro JL, Fragozo-Ramos MC, Milán AF, et al. Serum levels of myonectin are lower in adults with metabolic syndrome and are negatively correlated with android fat mass. Int J Mol Sci 2023;24:6874.
114. Sini ZK, Afzalpour ME, Ahmadi MM, et al. Comparison of the effects of high-intensity interval training and moderate-intensity continuous training on indices of liver and muscle tissue in high-fat diet-induced male rats with non-alcoholic fatty liver disease. Egyptian Liver J 2022;12:63.
115. Gamas L, Matafome P, Seiça R. Irisin and myonectin regulation in the insulin resistant muscle: implications to adipose tissue: muscle crosstalk. J Diabetes Res 2015;2015:359159.
116. Sabag A, Barr L, Armour M, et al. The effect of high-intensity interval training vs moderate-intensity continuous training on liver fat: a systematic review and meta-analysis. J Clin Endocrinol Metab 2022;107: 862-81.

Disclaimer

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article or claim that may be made by its manufacturer is not guaranteed or endorsed by the publisher.

Submitted: 10 November 2024.
Accepted: 1 July 2025.
Early access: 23 July 2025.