



Review

Interaction between sarcopenia and nonalcoholic fatty liver disease

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Sarcopenia and nonalcoholic fatty liver disease (NAFLD) are common health problems related to aging. Despite the differences in their diagnostic methods, several cross-sectional and longitudinal studies have revealed the close link between sarcopenia and NAFLD. Sarcopenia and NAFLD are linked by several shared pathogenetic mechanisms, including insulin resistance, hormonal imbalance, systemic inflammation, myostatin and adiponectin dysregulation, nutritional deficiencies, and physical inactivity, thus implicating a bidirectional relationship between sarcopenia and NAFLD. However, there is not sufficient data to support a direct causal relationship between sarcopenia and NAFLD. Moreover, it is currently difficult to conclude whether sarcopenia is a risk factor for nonalcoholic steatohepatitis (NASH) or is a consequence of NASH. Therefore, this review intends to touch on the shared common mechanisms and the bidirectional relationship between sarcopenia and NAFLD. (*Clin Mol Hepatol* 2023;29(Suppl):S68-S78)

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INTRODUCTION

The global epidemic of obesity and metabolic syndrome in an aging population has led to growing health problems including nonalcoholic fatty liver disease (NAFLD) and sarcopenia. Sarcopenia is defined as the progressive and generalized loss of skeletal muscle mass, strength, and/or function with a risk of adverse outcomes such as physical disability, hospitalization, and mortality.^{1,2} Despite the differences in their diagnostic methods, several studies have revealed the close link between sarcopenia and NAFLD.³⁻¹⁶ This review focuses on the shared mechanisms and a bidirectional relationship between sarcopenia and NAFLD.

OPERATIONAL DEFINITION OF SARCOPENIA

Sarcopenia, previously considered an aging-related syndrome, is now recognized as a progressive disease associated with type 2 diabetes mellitus (T2DM), metabolic syndrome, liver disease, and cardiovascular disease.¹⁷⁻²⁰ It is primarily associated with aging and secondarily with diseases mediated by systemic inflammation and insulin resistance (IR).²¹ In 2018, the European Working Group on Sarcopenia in Older People defined sarcopenia by low levels across three parameters: muscle strength, muscle quantity/quality, and physical performance. The presence of low muscle strength is the primary parameter to suspect sarcopenia, while the presence of

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low muscle mass (quantity) and quality are confirmatory. The coexistence of these factors represents severe sarcopenia.² Therefore, all these parameters enable improved understanding and awareness of sarcopenia.

SHARED MECHANISMS OF SARCOPENIA AND NAFLD

Sarcopenia and NAFLD share common underlying mechanisms, including IR, hormonal imbalance, systemic inflammation, myostatin and adiponectin dysregulation, nutritional deficiencies, and physical inactivity (Fig. 1).²²

Insulin resistance

IR is the main pathologic mechanism causing both sarcopenia and NAFLD. IR results from the loss of skeletal muscle mass. It causes increased lipolysis with the consequent release of free fatty acids (FFA) from adipose tissue. IR also inhibits growth hormone (GH)/insulin growth factor-1 (IGF-1) axis that normally plays a protective role in muscle regeneration and age-related muscle loss.^{17,23,24} It causes compensatory hyperinsulinemia, which leads to promotion of gluconeogenesis, upregulation of sterol regulatory element binding

protein 1c, inhibition of β -oxidation, increased FFA delivery, and altered triglyceride (TG) transport. These events leads to accumulation of TGs in skeletal muscle and the liver, often referred to as ectopic fat.^{25,26}

Impaired suppression of gluconeogenesis promotes proteolysis and reduces protein synthesis,⁷ which results in age-related muscle depletion and sarcopenia.²⁷⁻²⁹ Insulin activates the mammalian target of rapamycin (mTOR), 4E-binding protein 1, and ribosomal S6 kinase 1. These are involved in protein synthesis, maintenance of muscle mass, and skeletal muscle anabolism.³⁰ Skeletal muscle IR leads to increased muscle degradation with decreased mitochondrial content, function, and oxidative capacity.³¹ A study demonstrated that T2DM was independently associated with sarcopenia, leading to metabolic disorders and physical disability in older adults with T2DM.³² Furthermore, sarcopenia aggravates IR, since skeletal muscle is a primary insulin-responsive organ.³³ Likewise, myosteatosis, defined as fatty infiltration of muscle, is associated with reduced muscle function, IR, and a high risk of mortality in cirrhotic patients.^{34,35} Both sarcopenia and obesity simultaneously induce more severe IR and glycemic dysregulation.³³

Chronic inflammation

Inflammation and oxidative stress have been linked to the pathogenesis of NAFLD. Intramuscular lipid accumulation induces the secretion of proinflammatory cytokines from adipose tissue and generates oxygen-free radicals in the liver by inhibiting mitochondrial function for β -oxidation, leading to lipid peroxidation. Cytokines, such as interleukin-6 (IL-6), tumor necrosis factor- α (TNF- α), and transforming growth factor- β (TGF- β) induce chronic low-grade inflammation.^{36,37} Compared to healthy subjects, patients with isolated steatosis and steatohepatitis had increased TNF- α levels.³⁸ TNF- α causes lipid accumulation in the liver through activation of *de novo* lipogenesis (DNL).³⁹ It also stimulates nuclear factor κ B, the main transcriptional factor for proinflammatory cytokines that contribute to the development of NAFLD and muscle catabolism.^{36,39,40} Catabolic inflammation further worsens

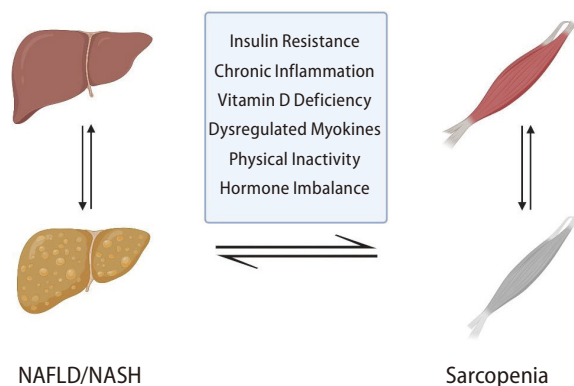


Figure 1. Bidirectional relationship between sarcopenia and NAFLD. NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.

Abbreviations:

CRP, C-reactive protein; FFA, free fatty acid; GH, growth hormone; IGF-1, insulin growth factor-1; IL-6, interleukin-6; IR, insulin resistance; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; TG, triglyceride; T2DM, type 2 diabetes mellitus; TGF- β , transforming growth factor- β ; TNF- α , tumor necrosis factor- α ; VDR, vitamin D receptor

sarcopenia among older patients because of the release of numerous inflammatory mediators from immune cells and adipocytes that contribute to the development of IR.⁴¹ Patients with sarcopenia demonstrate chronic inflammation, increased levels of C-reactive protein (CRP) and proinflammatory cytokines, and decreased levels of anti-inflammatory cytokines.³ IL-6 and CRP levels are also positively associated with total body fat mass and inversely associated with appendicular lean body mass.^{4,42}

Vitamin D

Vitamin D is involved in the modulation of IR, NAFLD, metabolic syndrome, and sarcopenia.⁴³ It plays an essential role in myogenesis, myoblast proliferation and differentiation, production and growth of skeletal muscle cells, and skeletal muscle inflammation.⁴⁴⁻⁴⁷ It exerts its effects through the nuclear vitamin D receptor (VDR), which is expressed in the liver and skeletal muscle.^{48,49} Downregulation of VDR expression by vitamin D deficiency and aging may lead to sarcopenia.³⁶ Studies show that subjects with sarcopenia have significantly lower vitamin D levels.^{6,50} Decreased levels of vitamin D are associated with decreased muscle strength, poor muscle function, and an increased risk of sarcopenia among older adults.⁵¹ However, vitamin D supplementation increases VDR expression in skeletal muscle, preventing the development of sarcopenia.⁵²

The relationship between vitamin D and NAFLD has been already acknowledged. A meta-analysis including 17 cross-sectional and case-control studies showed that patients with NAFLD had decreased levels of serum vitamin D.⁴³ Hypovitaminosis D was strongly associated with the presence of NAFLD independent of metabolic syndrome, T2DM, and IR.⁵⁰

Furthermore, vitamin D downregulates the expression of SREBP-1c, acetyl-coenzyme A carboxylase, and fatty acid synthase that modulate DNL, while peroxisome proliferator-activated receptor α and carnitine palmitoyltransferase-1 that mediate hepatic fatty acid oxidation are upregulated by vitamin D.⁵³ An animal study demonstrated that vitamin D deficiency worsened NAFLD by activating the inflammation-mediated pathway.⁴³ Vitamin D deficiency also causes IR via upregulation of hepatic IR, inflammatory, and oxidative stress genes.^{54,55} Moreover, VDR-knockout mice spontaneously developed hepatic steatosis.⁵⁵ Most studies, to date, have shown that vitamin D plays a pivotal role in the development

of sarcopenia and NAFLD. On the contrary, other studies demonstrated no significant relationship between vitamin D level and NAFLD/sarcopenia.^{56,57}

Myokines

Skeletal muscle is an endocrine organ that releases myokines^{58,59} after muscle contraction or strength training.⁶⁰ Myokines are involved in the autocrine regulation of muscle metabolism and the paracrine/endocrine regulation of other tissues and organs including the liver, adipose tissue, and brain.⁶¹⁻⁶³

Myostatin, a member of the TGF- β family, is predominantly expressed in skeletal muscles.^{64,65} It is an inhibitor of muscle mass and a key regulator of adipogenesis.⁶⁵⁻⁶⁸ It mediates Smad 2/3 activation, inhibiting myogenesis and protein synthesis by suppressing the Akt-mediated mTOR signaling pathway.⁶⁹ This causes muscle atrophy. Muscle proteolysis is stimulated through FoxO-dependent activation of the ubiquitin-proteasome pathway and autophagy.⁶⁹ Myostatin also increases adipose tissue mass and inhibits adiponectin secretion.^{22,70,71} Animal studies have demonstrated that blockage of myostatin significantly increases muscle mass, improves insulin sensitivity, and protects against liver steatosis.^{72,73} Animal models have demonstrated increased expression of activin type IIB, a myostatin receptor expressed in stellate cells, in liver fibrosis.^{74,75} Stellate cell cultures exposed to myostatin increase the expression of profibrotic proteins.⁷⁶ Therefore, myostatin, IR, and liver fibrogenesis are interconnected.

Irisin, an exercise-induced myokine, is inversely associated with the degree of fatty liver in obese patients and is a potential cause of sarcopenia and NAFLD. It increases energy expenditure through peroxisome proliferator-activated receptor α -dependent downstream signaling and improves insulin sensitivity and hepatic steatosis by upregulating fibroblast growth factor-21; these effects were independent of reduction in body weight and adiposity in a mouse model.^{77,78} It increases glucose uptake by enhancing glucose transporter type 4 translocation and β -oxidation of FFA through AMP-activated protein kinase activation in muscle cells.⁷⁹ Irisin expression in muscle and serum irisin level are reduced in obese subjects.⁸⁰

IL-6 has a dual metabolic effect. Muscle contractions stimulate acute IL-6 release from muscles,^{81,82} with the levels increasing as the duration and intensity of muscle contraction

increase.^{83,84} IL-6 improves hepatic gluconeogenesis, lipolysis in adipose tissue, pancreatic β -cell viability, and insulin secretion.^{81,85,86} It also enhances glucose uptake and fatty acid oxidation through adenosine monophosphate-activated protein kinase (AMPK) and phosphoinositide 3-kinase signaling processes.^{87,88} However, IL-6 acts as a pro-inflammatory cytokine in chronic inflammatory states such as obesity, infection, and cancer.⁸⁹ A study have demonstrated that increased IL-6 levels are associated with NASH, hepatic fibrosis, and IR.⁹⁰

Physical inactivity

The lack of physical activity causes loss of muscle mass and reduces energy consumption, resulting in obesity and hepatic steatosis.⁹¹ Both sarcopenia and NAFLD are worsened by chronic inflammation, oxidative stress, and IR.⁹² During exercise, production of pro-inflammatory cytokines is decreased while anti-inflammatory cytokine production, muscle protein synthesis, regeneration, and glucose uptake are increased. Physical activity mitigates the risk of sarcopenia progression.⁹³ Exercise can improve metabolic health status even without significant weight loss.⁹⁴

Other mechanisms

Adiponectin, a hormone secreted from adipose tissue, mediates glucose and lipid metabolism in insulin-sensitive tissues such as liver and muscle. In the liver, adiponectin promotes glucose use and enhances fatty acid oxidation by improvement of insulin action via activation of AMPK.^{95,96} In addition, adiponectin has an anti-inflammatory effect by neutralizing TNF- α , and improves hepatic steatosis and inflammation.⁹⁷

Anabolic hormones, such as GH and IGF-1, decline with aging process, which affects the progressive loss of muscle mass.⁹⁸ Fat accumulation and aging impair the GH/IGF-1 signaling pathway, leading to deterioration of muscle mass synthesis.^{99,100} In an experiential mouse model of NAFLD, NAFLD was associated with decreased muscle mass and strength, and reduced IGF-1 level, implicating that IGF-1 reduction might play a role in the development of NAFLD-related sarcopenia.¹⁰¹

BIDIRECTIONAL RELATIONSHIP BETWEEN SARCOPENIA AND NAFLD

Numerous studies have reported a relationship between NAFLD and sarcopenia (Tables 1, 2). Sarcopenia is a risk factor for the presence and severity of NAFLD (Table 1).^{7,22,102,103} The prevalence of sarcopenia is significantly increased in NAFLD and NASH compared to that in non-NAFLD (17.9% and 35.0% vs. 8.7%, respectively).³ NAFLD patients with sarcopenia had a 2-fold higher risk of developing NASH and significant fibrosis independent of obesity and IR.³ However, most studies were cross-sectional in design and the causal relationship between sarcopenia and NAFLD remains unclear. A recent study demonstrated that NAFLD was developed in 14.8% of its participants during a 7-year follow-up, with an increased incidence in participants with the lowest tertile of skeletal muscle mass at baseline. Baseline skeletal muscle mass was also positively associated with the resolution of existing NAFLD, regardless of metabolic risk factors.¹⁰ Sarcopenia was associated with poor clinical outcomes, including severe hepatic fibrosis and increased mortality, in NAFLD patients.¹⁰⁴⁻¹⁰⁶ Hence, low skeletal muscle mass may cause the development of NAFLD. In a multicenter prospective study, hepatic steatosis at baseline was significantly associated with the risk of sarcopenia in older adults. Lower muscle mass and strength were more common in NAFLD patients.¹⁶ In another study, the loss of skeletal muscle mass was faster in subjects with NAFLD compared to those without NAFLD. When stratified by fibrosis severity, skeletal muscle mass loss was faster in NAFLD subjects with an intermediate-to-high probability of advanced fibrosis than in those without (Table 2).¹⁰⁷

Muscle quality also plays a critical role in the development of NASH. Myosteatorosis determines muscle strength and function, and metabolic and liver-related clinical outcomes.¹⁰⁸⁻¹¹⁰ It is a prognosticator for NASH development.^{108,111,112} Studies have suggested that myosteatorosis is a clinically useful surrogate marker for NASH¹⁰⁸ by demonstrating that severe myosteatorosis, but not sarcopenia, predicts NASH development and fibrosis progression.¹¹¹ The prevalence of myosteatorosis is increased in obese subjects with NASH; hence, myosteatorosis could reflect the histological features of NASH.¹¹⁰ Muscle alterations are linked with fibrosis severity in subjects with NAFLD.^{3-5,9,22,113-117} These suggest that the role of sarcopenia in NASH development is unclear. Both sarcopenia and myosteatorosis have been linked to advanced fibrosis and cirrho-

Table 1. Studies of sarcopenia as a risk factor for NAFLD

Study (yr)	Study design	Study size	Study population	Sarcopenia assessment	NAFLD assessment	Study conclusion
Hong et al. (2014) ⁴	Cross-sectional	526	Korean	DXA	CT	5-fold increased risk of NAFLD
Lee et al. (2015) ⁶	Cross-sectional	15,132	Korean	DXA	Noninvasive models	2.3- to 3.3-fold increased risk of NAFLD in patients with sarcopenia
Lee et al. (2016) ⁷	Cross-sectional	2,761	Korean	DXA	Noninvasive models	2-fold increased risk of fibrosis in patients with sarcopenia
Kim et al. (2016) ⁸	Cross-sectional	3,739	Korean	DXA	Noninvasive models	Low SMI is associated with NAFLD according to age group and menopause status
Koo et al. (2017) ³	Cross-sectional	309	Korean	BIA	Liver biopsy	Increased prevalence of sarcopenia with NAFLD severity 2.5-fold increased risk of NASH and significant fibrosis in patients with sarcopenia
Petta et al. (2017) ⁹	Cross-sectional	225	Italian	BIA	Liver biopsy	2-fold increased risk of fibrosis in NAFLD in patients with sarcopenia
Zhai et al. (2018) ¹²	Cross-sectional	494	Chinese	DXA	US	NAFLD is not independently associated with sarcopenia.
Kim et al. (2018) ¹⁰	Longitudinal	10,534	Korean	BIA	Noninvasive models	Increased incidence of NAFLD in patients with sarcopenia Increased resolution of baseline NAFLD with higher muscle mass
Wijarnpreecha et al. (2019) ¹³	Cross-sectional	11,325	American	BIA	US	2.3-fold increased risk of NAFLD in patients with sarcopenia 1.8-fold increased advanced fibrosis in patients with sarcopenia
Hsieh et al. (2021) ¹⁰⁴	Cross-sectional	521	Korean	CT	Liver biopsy	Increased risk of significant fibrosis in NAFLD
Hsieh et al. (2022) ¹¹¹	Longitudinal	338	Korean	CT	Liver biopsy	Severe myosteatosis is significantly associated with early NASH and fibrosis progression in early stage NAFLD

NAFLD, nonalcoholic fatty liver disease; DXA, dual energy X-ray absorptiometry; CT, computed tomography; SMI, skeletal muscle index; BIA, Bioelectric impedance analysis; NASH, nonalcoholic steatohepatitis; US, ultrasonography.

Table 2. Studies of NAFLD as a risk factor for sarcopenia

Study (yr)	Study design	Study size	Study population	Sarcopenia assessment	NAFLD assessment	Study conclusion
Issa et al. (2014) ⁵	Cross-sectional	75	American	CT	Liver biopsy	Increased risk of sarcopenia in NASH and NASH cirrhosis
Sinn et al. (2022) ¹⁰⁷	Longitudinal	52,815	Korean	BIA	US	Faster loss of skeletal muscle mass in NAFLD Much faster loss of skeletal muscle mass in NAFLD according to fibrosis severity
Roh et al. (2022) ¹⁶	Longitudinal	1,595	Korean	DXA	Noninvasive models	Increased risk of developing LMM (1.65-fold) and LMS (2.29-fold) in NAFLD

NAFLD, nonalcoholic fatty liver disease; CT, computed tomography; NASH, nonalcoholic steatohepatitis; BIA, Bioelectric impedance analysis; US, ultrasonography; DXA, dual energy X-ray absorptiometry; LMS, low muscle strength; LMM, low muscle mass.

sis.^{22,34,118-121} However, the relatively low skeletal muscle mass observed in NAFLD patients may derive from increased body fat percentage.^{15,110} Muscle wasting is often seen in patients with advanced fibrosis, implicating reverse causality between low skeletal muscle mass and NAFLD severity.^{9,14} Patients with liver cirrhosis had concomitant sarcopenia (43%), sarcopenic obesity (low muscle mass with obesity) (26%), and myosteatosis (52%).³⁴ Hence, advanced fibrosis is more likely to cause sarcopenia rather than sarcopenia causing fibrosis progression.

CONCLUSIONS

It is currently difficult to conclude whether sarcopenia is a risk factor or a consequence of NASH. However, sarcopenia and NAFLD are linked by several shared pathogenetic mechanisms, implicating a bidirectional relationship between sarcopenia and NAFLD. Therefore, further studies are needed to investigate the effects of low muscle function and performance on NAFLD progression. In addition, prospective standardized trials with accurate diagnoses of sarcopenia and NAFLD are warranted to elucidate the cause-and-effect relationship between sarcopenia and NAFLD.

Authors' contribution

Sae Kyung Joo: drafting the manuscript; preparation of the figure and table. Won Kim: design of the work; supervision of the article; obtaining funding.

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Conflicts of Interest

The authors have no conflicts to disclose.

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