REVIEW ARTICLE

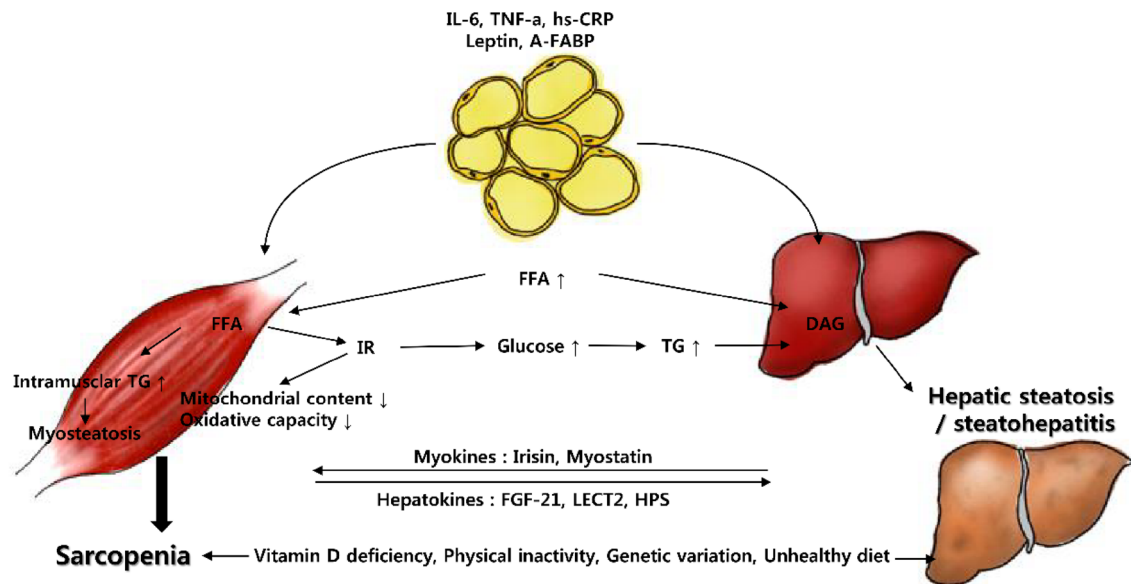# Sarcopenia and fatty liver disease

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Abstract

Non-alcoholic fatty liver disease (NAFLD) is the most common liver disease which may progress to non-alcoholic steatohepatitis. The prevalence of sarcopenia, which is the loss of muscle mass and strength, is increasing in the aging society. Recent studies reported the relationship between NAFLD and sarcopenia. The skeletal muscle is the primary organ for glucose disposal. Loss of muscle mass can cause insulin resistance, which is an important risk factor for NAFLD. Moreover, obesity, chronic low-grade inflammation, vitamin D deficiency, physical inactivity, hepatokines, and myokines might be involved in the pathophysiologic mechanism of sarcopenia and NAFLD. Although most of the previous studies have demonstrated the positive correlation between sarcopenia and NAFLD, the difference in diagnostic methods of sarcopenia and NAFLD leads to difficulties in interpretation and application. This review discusses the concept and diagnosis of sarcopenia and NAFLD, common pathophysiology, and clinical studies linking sarcopenia to NAFLD. The presentation of the association between sarcopenia and NAFLD may provide an opportunity to prevent the deterioration of fatty liver disease.

Graphic abstract

Keywords Sarcopenia · Skeletal muscle · Non-alcoholic fatty liver disease · Liver · Pathophysiology

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Introduction

Sarcopenia is an age-related decrease in muscle mass with progressive loss of muscle strength and physical performance. It is associated with metabolic impairment, falls, disability, hospitalization, and mortality in the elderly [1]. Besides aging, sarcopenia can occur earlier in life secondary to various causes, including unhealthy diet, physical inactivity, and chronic diseases [2]. The skeletal muscle is the primary organ of insulin-mediated glucose disposal, decreased muscle mass has a pivotal role in insulin resistance (IR) and metabolic syndrome [3].

Non-alcoholic fatty liver disease (NAFLD) is the most common liver disease worldwide, with a prevalence of 25.2% globally, 24% in the USA, and 27% in Asia [4]. The prevalence of NAFLD is gradually increasing, and the prevalence of NAFLD and non-alcoholic steatohepatitis (NASH) would increase by 21% and 63%, respectively, from 2015 to 2030. Moreover, NAFLD affecting 10–20% of the general pediatric population, the prevalence of NAFLD will rise more rapidly [5]. NAFLD can progress from simple steatosis to NASH and can be accompanied by liver cirrhosis, and liver failure [6]. NAFLD is associated with IR, type 2 diabetes mellitus (T2DM), cardiovascular disease, and significantly higher mortality than in the general population [7].

The main pathophysiology of sarcopenia is associated with insulin resistance, which plays a major role in the development of NAFLD. The prevalence of sarcopenia is higher in patients affected by NAFLD and correlates with the severity of fatty liver disease. In a recent meta-analysis, the risk of NAFLD and NAFLD-related fibrosis was higher in subjects with sarcopenia than in subjects without sarcopenia (29% and 57%, respectively) [8]. Loss of muscle mass is associated with decreased survival, increase in the length of hospitalization, and mortality in patients with cirrhosis [9]. Moreover, muscle function is related to NAFLD and vice versa. To clearly elucidate the interaction between sarcopenia and NAFLD, it is important to clarify definition and diagnosis. In this review, we described the definition and diagnostic methods of NAFLD and sarcopenia, then summarize the results of recent clinical studies and suggest possible pathological mechanisms. Furthermore, the role of hepatokines and myokines in the crosstalk between skeletal muscle and liver is introduced.

NAFLD

NAFLD is a spectrum of liver diseases encompassing non-alcoholic fatty liver (NAFL), NASH, fibrosis, and cirrhosis in the absence of excessive alcohol consumption (> 20 g/day for Female and > 30 g/day for male). NAFL is defined as ≥ 5% of steatosis without hepatocellular injury. NASH is defined as steatosis with hepatocellular damage with or without hepatic fibrosis. NAFLD is closely related to visceral obesity, IR, T2DM, hypertension, and dyslipidemia; and has been regarded as a hepatic manifestation of metabolic syndrome [10]. Hepatic steatosis development is regulated by increased free fatty acids (FFA) from the adipose tissue or dietary intake, hepatic de novo lipogenesis, impaired fatty acid oxidation, and decreased liver secretion [11]. The mechanism of liver injury in NAFLD is currently thought to be a "multiple hit process" involving IR, oxidative stress, apoptosis, and adipokines [12]. A sedentary lifestyle with a high-caloric diet, excess saturated fat, refined carbohydrate, and high fructose intake have been associated with obesity and NAFLD [13].

Liver biopsy is regarded as the gold standard for diagnosing NAFLD. However, ultrasonography is recommended as the first-line imaging modality in a clinical setting as it is easily accessible and relatively accurate in diagnosing hepatic steatosis compared to histology (sensitivity of 85% and specificity of 94%) [14]. A controlled attenuation parameter is a promising tool for non-invasive detection of hepatic steatosis along with liver stiffness [15]. It is measured by vibration-controlled transient elastography with FibroScan® and is comparable with biopsy-diagnosed steatosis (sensitivity of 69% and specificity of 82%). ^{1}H-magnetic resonance spectroscopy is a safe and non-invasive alternative for quantification of hepatic fat content that offers good reproducibility [16]. Besides imaging modalities, risk factor models, such as SteatoTest, fatty liver index, NAFLD liver fat score, hepatic steatosis index, and Framingham steatosis index, can also be used for estimation of hepatic steatosis. In case of NASH, liver biopsy remained the most specific test to define the characteristics and severity of the liver disease. The NAFLD fibrosis score, fibrosis-4 index, enhanced liver fibrosis test, and Fibrotest can be used to define fibrosis using a non-invasive method [17].

Sarcopenia

Definition and diagnosis of sarcopenia

Sarcopenia was first described in 1989, and is derived from the Greek words "*sarx*" meaning flesh and "*penia*" meaning loss [18]. Sarcopenia is defined as appendicular skeletal muscle mass (ASM) divided by height in square meters (ASM/height^2) less than two standard deviations (SD) below the mean for young reference group [19]. ASM/height^2 is the most commonly used method adopted by the European Working Group on Sarcopenia in Older People (EWGSOP), International Working Group on

Sarcopenia, and Asian Working Group for Sarcopenia (AWGS) guidelines [1, 20, 21]. This operational method has a significant correlation with physical disability [19]. However, this is highly correlated with body mass index (BMI), the current index for obesity, which considers thin people as sarcopenic and underestimates sarcopenia in overweight or obese people. In 2002, the weight-adjusted muscle mass index was developed [22]. This index was modified as ASM/weight and is wildly used in investigating the relationship between sarcopenia and metabolic diseases, such as metabolic syndrome, NAFLD, and diabetes [23]. In 2010, EWGSOP proposed an operational clinical definition and consensus on the diagnostic criteria [20]. The working definition of sarcopenia was required to consider muscle mass, strength, and physical performance for the first time. Based on the EWGSOP guidelines, AWGS published a sarcopenia consensus report for Asians containing an algorithm for the diagnosis and unique cutoff points of each parameter [21]. Recently, the Foundation for the National Institutes of Health (FNIH) Sarcopenia Project published a consensus definition of sarcopenia using a database from nine large observational studies with more than 25,000 participants. Since obesity influences the relationship between lean mass and muscle strength, FNIH created an alternative, the skeletal muscle index (SMI), which is defined as ASM/BMI [24]. We found that ASM/BMI-defined sarcopenia is more closely related to IR index, visceral obesity, and metabolic syndrome than other muscle mass indices in the Korean population [25]. There is no current unified definition for sarcopenia because of different clinical implications according to the consensus on sarcopenia.

In 2018, EWGSOP2 updated the sarcopenia definition and care strategy [2]. In these guidelines, muscle strength is the principal parameter of sarcopenia. After low muscle strength is detected, low muscle quantity or quality confirms sarcopenia. Additionally, FNIH and AWGS considered muscle strength in the first place for diagnosing sarcopenia. Based on the new consensus and research data, incorporating muscle strength/physical performance along with low muscle mass in defining sarcopenia is crucial in elucidating the association between sarcopenia and NAFLD.

Sarcopenia is primarily associated with aging in elderly people, but it can be due to secondary causes. EWGSOP2 suggests the concept of secondary sarcopenia, which is caused by loss of muscle mass and function secondary to malignancy, organ failure, physical inactivity, and inadequate energy intake [2]. In addition, the AWGS consensus suggests screening of sarcopenia not only in the elderly, but also in people with specific clinical conditions, such as the presence of recent functional decline or impairment, unintentional weight loss, depression or cognitive disorder, repeated falls, malnutrition, and chronic conditions (chronic heart failure, diabetes mellitus, chronic kidney disease, and other chronic wasting conditions) [21].

Assessment of sarcopenia

Muscle mass can be measured as total body skeletal muscle mass, ASM, and cross-sectional area of a specific body site or muscle group. Dual-energy X-ray absorptiometry is the most commonly used method for muscle measurement in sarcopenia. Body impedance analysis (BIA) has been widely used as an alternative method, because it is non-invasive and easily accessible, cost-effective, and has radiation-free characteristics. However, BIA is less validated and easily altered based on temperature, humidity, and water contents. Hence, diagnostic accuracy has not been fully established. Computed tomography and magnetic resonance imaging have been considered as the gold standards for evaluation of body composition [26]. The psoas, paraspinal, and abdominal muscles in the third lumbar vertebra region are the most common muscles used for estimating muscle mass indices [27]. In addition, ultrasonography may measure muscle mass and quality. The handgrip strength is considered as a reliable and convenient method to measure muscle strength [28]. Grip strength is a predictor of strength in other body compartments, the length of hospital stay, functional limitations, quality of life, and death [29]. Likewise, the chair rise test can be used to measure the strength and endurance of leg muscles. Physical performance can be assessed using gait speed, short physical performance battery (SPPB), and Timed Up and Go test [20]. Gait speed is commonly adopted in the EWGSOP, AWGS, and FNIH guidelines.

Prevention and treatment approaches to sarcopenia

There are no approved pharmacological interventions for sarcopenia. The main strategy for prevention and treatment of sarcopenia is lifestyle intervention, such as exercise and nutrition. Resistance training improves physical strength and muscle mass by increasing type II muscle fiber size and satellite muscle recruitment. Aerobic exercise remodels myofibers and improves cardiorespiratory fitness. Besides lifestyle intervention, proper nutritional support (protein, essential amino acid, β-hydroxy-β-methylbutyrate, Vit. D, creatinine, etc.) is crucial in sarcopenia; and the benefit of exercise is potentiated with nutritional support. In Japanese sarcopenic female, exercise with amino acid supplementation enhanced muscle strength, muscle mass, and walking speed [30]. In addition, a calorie restriction regimen with exercise may be a good option for the treatment of obese sarcopenic subjects [31]. In light of the close relationship between obesity and NAFLD, calorie restriction with exercise might be the efficient strategy to interrupt for the vicious cycle of sarcopenia and NAFLD.

Clinical studies

Clinical studies on the association between sarcopenia and NAFLD/NASH are summarized in Table 1. Most studies were conducted in Asia [32–42] and only four studies [43–46] were analyzed from other continents. Currently, most studies show a positive relationship between sarcopenia and NAFLD.

In 2014, we investigated the relationship between sarcopenia and NAFLD from the Korean Sarcopenic Obesity Study [32]. Subjects with low muscle mass had an increased risk of NAFLD after adjusting for IR and inflammation. SMI had reverse association with HOMA-IR, hs-CRP, triglycerides, and total body fat. Moreover, subjects with the lowest quartile of SMI value had a higher risk of NAFLD even after adjusting for potential confounding factors. Another subsequent study showed a positive relationship between sarcopenia and NAFLD regardless of obesity or IR [33]. Furthermore, they presented that sarcopenic subjects with NAFLD had a higher risk of advanced fibrosis than normal subjects, independent of obesity, IR, or liver enzyme levels [34]. A 1% increment in SMI could decrease the risk of NAFLD by 20% in men with T2DM [36], and the grip strength was inversely related to NAFLD [40].

The association of sarcopenia and NAFLD is closely related to the severity of the advanced fatty liver disease. One study from Korea showed that the prevalence of sarcopenia gradually increased from control to NAFLD and NASH groups [8.7%, 17.9%, and 35.0%, respectively ($p < 0.001$)] [37]. Furthermore, sarcopenic subjects with NAFLD had increased risk of NASH (OR 2.30; 95% CI 1.08–4.93) and significant fibrosis (OR 2.05; 95% CI 1.01–4.16) independent of obesity and IR. Another two studies support the relationship between sarcopenia and severity of NASH and liver fibrosis in Caucasians [44, 45]. Although most previous studies have demonstrated a consistently positive association between sarcopenia and NAFLD, two studies revealed a heterogeneous association. One study showed different associations between sarcopenia and NAFLD based on the criteria used for diagnosing sarcopenia [46], whereas another study reported no relationship between NAFLD and sarcopenia when sarcopenia was defined by muscle mass, muscle strength, and gait speed [41].

Since most studies were conducted using a cross-sectional design, the causal relationship between sarcopenia and NAFLD cannot be determined. Recently, in a 7-year follow-up, longitudinal cohort study including 15,567 subjects, which consisted of 12,624 subjects without NAFLD and 2943 subjects with NAFLD, showed that 14.8% of baseline non-NAFLD subjects developed NAFLD, and

subjects with the highest tertile of SMI at baseline had decreased risk of NAFLD (adjusted hazard ratio [AHR], 0.44; 95% CI, 0.38–0.51) [38]. Furthermore, a positive association in baseline SMI and the resolution of existing baseline NAFLD was noted. Interestingly, the study evaluated the association between the change in SMI in a year and NAFLD. The highest tertile of change in SMI showed a significantly decreased incidence of NAFLD (AHR 0.69; 95% CI 0.59–0.82) and resolution of baseline NAFLD (AHR 4.17; 95% CI 1.90–6.17) even after adjusting the baseline SMI. It was suggested that maintaining or increasing skeletal muscle mass could be a therapeutic option for NAFLD.

Pathophysiology

The possible mechanisms of interaction between NAFLD and sarcopenia are IR, obesity, chronic low-grade inflammation, physical inactivity, hepatokines, and myokines (Fig. 1, Table 2). The potential pathophysiological mechanisms are listed below.

Insulin resistance

IR is the main pathologic mechanism of sarcopenia and NAFLD. It is caused by fat tissue infiltration in the skeletal muscle and increased circulating FFA from excessive body fat [3, 47]. Insulin activates the mammalian target of rapamycin and enhances signaling to its downstream effectors 4E-binding protein 1 and ribosomal S6 kinase 1, which results in maintenance of muscle mass and plays a role in skeletal muscle anabolism [48]. Skeletal muscle IR leads to increased muscle degradation with decreased mitochondrial content, function and oxidative capacity [49]. Therefore, IR can be one of the pivotal mechanisms causing sarcopenia. We found that T2DM was independently associated with sarcopenia, leading to metabolic disorders and physical disability in older adults with T2DM [50]. Furthermore, reduced muscle mass may aggravate IR.

Skeletal muscle acts as the primary organ for whole-body glucose homeostasis by expression of insulin-dependent transporter GLUT-4 [51]. Decreased insulin sensitivity impairs glucose uptake and insulin stimulated glycogen synthesis [3]. Excess glucose is converted to triacylglycerol in the liver, causing NAFLD, which can be attributed to hepatic IR [52]. Moreover, obesity induces an increased flux of FFA, increased hepatic diacylglycerol concentration, and translocation of protein kinase-Cε (PKCε) to the plasma membrane, which inhibits tyrosine phosphorylation of receptor substrate (IRS)-1 and IRS-2, phosphoinositide 3-kinases activation, and hepatic insulin signaling [53]. Hence, both hepatic IR and peripheral IR can be pathologic mechanism for NAFLD.

Table 1 Characteristics and outcomes of the clinical studies of sarcopenia and NAFLD/NASH

Author (year)	Study design	Race	Study population (N)	Method to define sarcopenia	Method to define NAFLD	Method to define NASH/Fibrosis	Outcome	References
Hong et al. (2014)	Cross-sectional	Korean	Male (167) Female (285)	DXA SMI (total SMM (kg)/weight (kg)×100) SMI<1SD	CT LAI<5 HU		The lowest quartile of SMI had the highest risk of NAFLD (OR, 5.16)	[32]
Issa et al. (2014)	Cross-sectional	Caucasian	Total (75)	CT L4 vertebra psoas/paraspinal muscle		Liver biopsy	Prevalence of sarcopenia increased from control to NASH and NASH-cirrhosis groups	[43]
Lee et al. (2015)	Cross-sectional	Korean	Male (5617) Female (9515)	DXA SMI (total ASM (kg)/weight (kg)×100) SMI<1SD	HSI CNS LFS	BARD FIB-4	Sarcopenia and NAFLD had an independent association after adjusting for obesity or insulin resistance (OR, 1.18). Sarcopenia had a higher risk of advanced fibrosis	[33]
Hashimoto et al. (2016)	Cross-sectional	Japanese	Type 2 diabetes Male (79) Female (66)	DXA SMI (SMM (kg)/weight (kg)×100)	Transient elastography CAP		SMI was independently correlated with CAP in male. OR per 1SD of SMI for NAFLD was 0.80	[36]
Kim et al. (2016)	Cross-sectional	Korean	Male (1184) Female (2555)	DXA SMI (total ASM (kg)/weight (kg)×100)	FLI≥60		Low SMI associated with NAFLD. The association was different according to age group and menopause status	[35]
Lee et al. (2016)	Cross-sectional	Korean	Male (1241) Female (1520)	DXA Sarcopenia index (total ASM (kg)/BMI (kg/m^2) Male<0.789, Female<0.521	HSI CNS LFS	NFS FIB-4 Forns index	Sarcopenia had a significant association with liver fibrosis in subjects with NAFLD.	[34]

Table 1 (continued)

Author (year)	Study design	Race	Study population (N)	Method to define sarcopenia	Method to define NAFLD	Method to define NASH/Fibrosis	Outcome	References
Koo et al. (2017)	Cross-sectional	Korean	Male (145) Female (164)	BIA ASM/weight (total ASM (kg)/weight (kg) × 100) ASM/BMI (total ASM (kg)/BMI (kg/m^2))	Liver biopsy	Liver biopsy	Low muscle mass was associated with histological severity of NAFLD, sarcopenia was significantly associated with NASH and fibrosis, after adjusting for obesity, inflammation, and insulin resistance	[37]
Petta et al. (2017)	Cross-sectional	Italian	Male (141) Female (84)	BIA SMI (total ASM (kg)/weight (kg) × 100) SMI < 1SD	Liver biopsy	Liver biopsy	Sarcopenia was associated with severe steatosis (OR, 2.02) and severe fibrosis (OR, 2.36) in NAFLD patients	[44]
Meng et al. (2016)	Cross-sectional	Chinese	Male (10,679) Female (10,278)	Grip strength (kg)/weight (kg)	US		Grip strength was inversely associated with NAFLD	[40]
Zhai et al. (2018)	Cross-sectional	Chinese	Male (216) Female (278)	DXA ASM (kg)/height^2 (Male < 7.0 kg/m^2, Female < 5.4 kg/m^2) Hand grip strength (Male < 26 kg, Female < 18 kg) 6 m-usual gait speed < 0.8 m/s	US		Sarcopenia, defined according to muscle mass, grip strength, and gait speed, was not independently associated with NAFLD	[41]

Table 1 (continued)

Author (year)	Study design	Race	Study population (N)	Method to define sarcopenia	Method to define NAFLD	Method to define NASH/Fibrosis	Outcome	References
Kim et al. (2018)	Prospective	Korean	Male (9091) Female (6476)	BIA SMI (total ASM (kg)/weight (kg) × 100) SMI (total ASM (kg)/BMI (kg/m²))	HSI		Highest SMI tertile at baseline had an inverse association with NAFLD (HR, 0.44) and positive association with the resolution of NAFLD (HR, 2.09) Increased SMI over a year had a beneficial association with incident NAFLD (HR, 0.69) and resolution of baseline NAFLD (HR, 4.17)	[38]
Lee et al. (2019)	Retrospective, longitudinal	Korean	Male (2174) Female (2224)	BIA ASM (kg)	US		Decreased ASM was significantly associated with incident NAFLD in non-obese subjects	[39]
Wijarnpreecha et al. (2019)	Cross-sectional	US population	Male (5334) Female (5991)	BIA SMI (total ASM (kg)/weight (kg) × 100) SMI < 1SD	US	NFS	Sarcopenia was independently associated with NAFLD (OR 1.24) and advanced fibrosis (OR 1.79) with advanced fibrosis (OR 1.79)	[45]
Kang et al. (2019)	Cross-sectional	Korean	Male (5661) Female (5050)	BIA LSMM-BW (total ASM (kg)/weight (kg) × 100) LSMM-BMI (total ASM (kg)/BMI (kg/m²)	US	NFS FIB-4 index	Low skeletal muscle was associated with advanced fibrosis in NAFLD independent of metabolic risk factors	[42]

Table 1 (continued)

Author (year)	Study design	Race	Study population (N)	Method to define sarcopenia	Method to define NAFLD	Method to define NASH/Fibrosis	Outcome	References
Peng et al. (2019)	Cross-sectional	US population	60-75 years Male (1240) Female (1311)	BIA SMI (ASM (kg)/ weight (kg)×100) SMI (ASM (kg)/ height^2 (m^2)) Gait speed ($\leq$0.8 m/s)	US		NAFLD had an inverse association with height-adjusted SMI (OR, 0.63). In contrast, NAFLD had a positive association with weight-adjusted SMI (OR, 1.73)	[46]

DXA dual-energy X-ray absorptiometry, *SMI* skeletal muscle index, *SMM* skeletal muscle mass, *SD* standard deviation, *CT* computed tomography, *HU* hounsfiled unit, *LAI* liver attenuation index, *NAFLD* non-alcoholic fatty liver disease, *OR* odds ratio, *NASH* non-alcoholic steatohepatitis, *ASM* appendicular skeletal muscle, *HSI* hepatic steatosis index, *CNS* comprehensive *NAFLD* score, *LFS* NAFLD liver fat score, *FIB-4* fibrosis-4, *CAP* controlled attenuation parameter, *FLI* fatty liver index, *BMI* body mass index, *BIA* body impedance analysis, *US* ultrasonography, *HR* hazard ratio, *LSMM* low skeletal muscle mass, *NFS* NAFLD fibrosis score

Hepatic steatosis is related more to skeletal IR than hepatic IR in patients with NAFLD, supporting the pivotal role of skeletal muscle IR in the development of NAFLD [54].
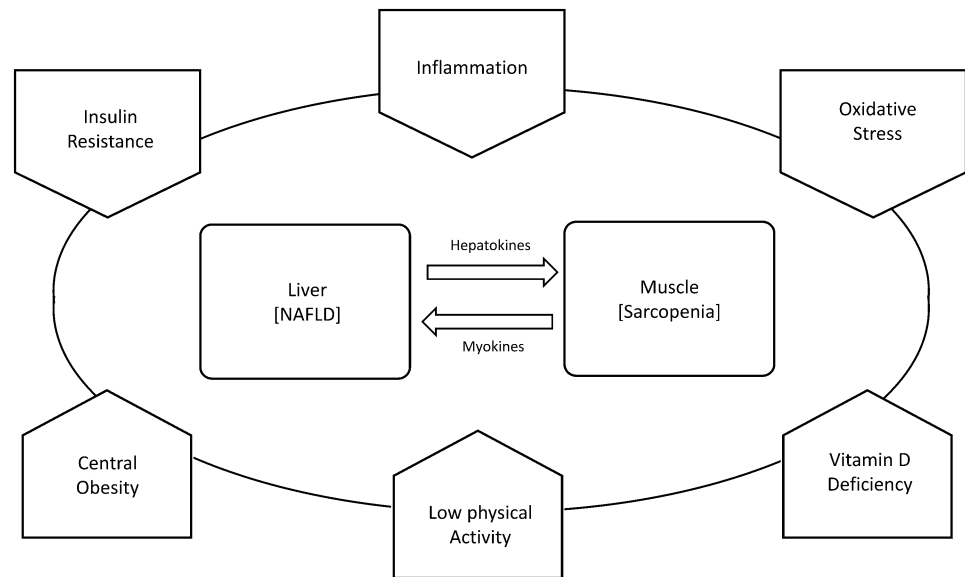
Obesity

Obesity is an important cause of the increasing global burden of metabolic and cardiovascular morbidity and mortality. The coexistence of sarcopenia and obesity is defined as sarcopenic obesity (SO). A reciprocal interaction between excess visceral fat and sarcopenia aggravates loss of muscle mass. In a longitudinal study, we revealed that visceral obesity was independently associated with future loss of skeletal muscle [55]. Adipose tissue–muscle–liver interplay causes NAFLD and accelerates liver fibrosis (Fig. 2). Especially, obesity-induced excess of FFA which results in liver damage and injury. Injured liver stimulates Kupffer cells and recruits monocyte-derived macrophages to accelerate the progression from NAFLD to NASH [56]. In addition, increased visceral adipose tissue promotes chronic inflammation by secreting inflammatory cytokines such as interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), plasminogen activator inhibitor-1, leptin, and other adipokines [57]. Leptin, the first adipocyte-secreted hormone, regulates appetite, energy metabolism, and body weight. However, hyperleptinemia can promote IR, hepatic inflammation, and fibrosis [58]. In the meta-analysis including 33 studies, circulating leptin levels were higher in NAFLD subjects than those in normal subjects, and leptin levels were positively correlated with NAFLD severity [59]. Another study demonstrated that ASM was independently and negatively correlated with the leptin level regardless of body fat mass [60]. Additionally, leptin upregulates proinflammatory cytokines and reduces the anabolic effect of insulin-like growth factor-1 (IGF-1) [61]. Moreover, visceral obesity itself strongly suppresses secretion of growth hormone (GH) by hyperinsulinemia, increases FFA and somatostatin tone, and reduces ghrelin. Impaired GH/IGF-1 axis could be associated with SO and ectopic fat deposition in the liver [62]. Adipocyte fatty acid-binding protein (A-FABP) can play a role in obesity-induced IR and inflammation. Serum A-FABP levels are negatively correlated with SMI (ASM/weight) independent of confounding factors [63]. In a cross-sectional study, A-FABP independently predicted the incidence of inflammation and fibrosis in NAFLD, even after adjusting the homeostasis model assessment-estimated insulin resistance (HOMA-IR) and visceral fat [64].

Vitamin D

Vit. D is the hormone involved in calcium homeostasis, bone metabolism, and muscle growth. It is known as a potent mediator of IR, metabolic syndrome, NAFLD, and

	Action	References
Hepatokines		
FGF-21	Reduces triglyceride level in the liver and skeletal muscle	[78, 79]
	Improvements in both hepatic and peripheral insulin sensitivity	
LECT2	Positively correlated with NAFLD	[80, 81]
	Mediates obesity and skeletal muscle IR	
Hepassocin	Promotes NAFLD	[83–85]
	Mediates skeletal muscle IR and type 2 diabetes	
Myokines		
Irisin	Improves hepatic steatosis and glucose metabolism	[87, 89, 90]
	Contradicting results in sarcopenia studies	
Myostatin	Negative effect on the skeletal muscle	[91, 92]
	Blocking myostatin increases muscle mass, insulin sensitivity and protects hepatic steatosis	

FGF-21 fibroblast growth factor–21, *LECT2* leukocyte cell-derived chemotaxin, *NAFLD* non-alcoholic fatty liver disease, *IR* insulin resistance

sarcopenia. This vitamin exerts its effect via the vitamin D receptor (VDR) expressed in various human cells including the skeletal muscle [65]. Vit. D deficiency reduces VDR expression, increases reactive oxygen species generation, and causes mitochondrial function disruption, leading to skeletal muscle atrophy [66]. Whole-body VDR knockout mice showed skeletal muscle dysfunction and abnormal development. In a 3-year longitudinal aging study, lower 25-OH Vit. D and higher parathyroid hormone levels increased the risk of sarcopenia in elderly people [67]. Subjects with 25-OH Vit. D < 25 nmol/L were 2.57 (95% confidence interval [CI], 1.40–4.70, based on grip strength) times and 2.14 (95% CI 0.73–6.33, based on muscle mass) times more likely to experience sarcopenia. Furthermore, Vit. D regulates oxidative stress, inflammation, hepatocyte apoptosis, and fibrosis in the liver [68]. In a cross-sectional study

in East China, 84.6% of male with NAFLD were diagnosed with Vit. D deficiency and subjects with decreased Vit. D levels had a 54% increased risk of NAFLD after adjusting confounding factors [69]. In a meta-analysis including 17 cross-sectional and case–control studies, NAFLD patients had decreased serum Vit. D levels and had a 26% increased risk of Vit. D deficiency (odds ratio [OR], 1.26; 95% CI 1.17–1.35) [70]. However, it is controversial whether or not Vit. D deficiency is related to the histologic feature of NAFLD [71, 72].

Chronic low-grade inflammation

Obesity induces increased levels of circulating inflammatory cytokines, including TNF-α, IL-6, and C-reactive protein (CRP), which cause chronic low-grade inflammation.

Fig. 2 Adipose tissue–muscle–liver interaction. *BM* bone marrow
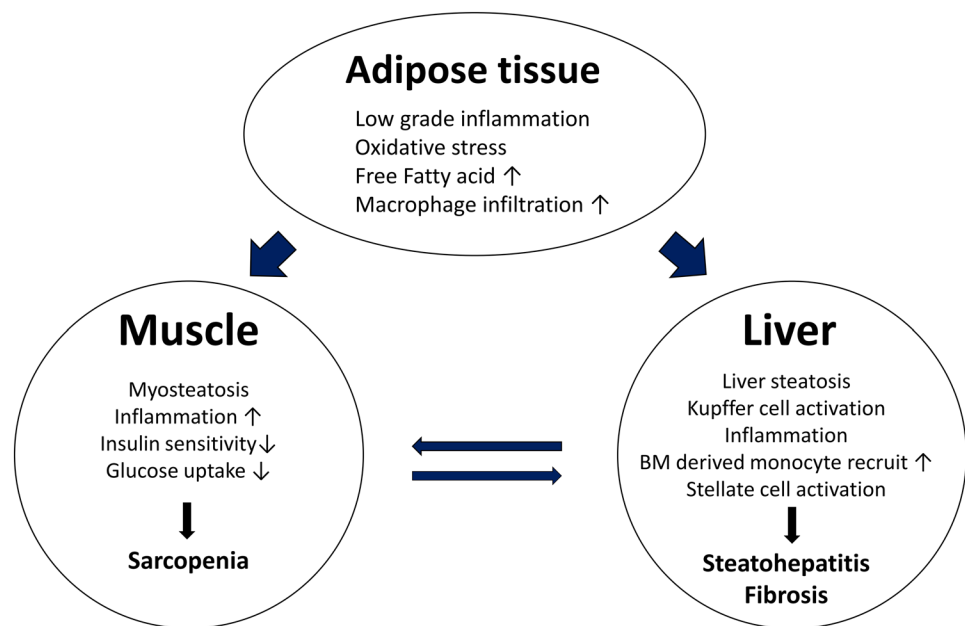
TNF-α stimulates reactive oxygen species production and causes oxidative stress and mitochondrial dysfunction [73]. It inactivates the AMP-activated protein kinase (AMPK) pathway, which leads to the development of NAFLD. The serum TNF-α level was higher in patients with simple steatosis and steatohepatitis than in healthy subjects [74]. IL-6 has an important role in the development of NASH and systemic inflammation; IL-6 levels were correlated with the degree of inflammation and fibrosis in the liver [75]. The above-mentioned inflammatory cytokines have a negative association with the skeletal muscle. In the Health ABC study, elevated TNF-α and IL-6 levels were correlated with low muscle mass and reduced muscle strength in aged male and Female [76]. In a 10-year longitudinal study, plasma TNF-α and IL-6 concentrations could predict the frailty and mortality in older subjects [77]. We demonstrated that subjects with sarcopenia had increased high-sensitivity C-reactive protein (hs-CRP) levels than subjects without sarcopenia. Moreover, hs-CRP levels had a negative correlation with SMI and liver attenuation index ($p < 0.001$) suggesting that inflammation may be an important causative factor of sarcopenia and NAFLD [32].

Hepatokines

Hepatokines are autocrine, paracrine, and endocrine proteins secreted by hepatocytes that can mediate metabolic disorders. These include adropin, angiopoietin-like protein 4, sex hormone-binding globulin, fetuin-A and -B, retinol-binding protein 4, selenoprotein P, fibroblast growth factor (FGF)-21, leukocyte cell-derived chemotaxin 2 (LECT2),

and hepassocin (HPS) [11]. In 2005, FGF-21 was first identified as a novel metabolic regulator. FGF-21 potentiates clearance of systemic glucose and lipids and improves insulin sensitivity, adiponectin action, mitochondrial function, thermogenesis, and energy expenditure. The improvement is correlated with a reduction in triglyceride and diacylglycerol levels and PKC translocation in the liver and skeletal muscle [78]. Infusion of FGF-21 in mouse model caused improvements in both hepatic and peripheral insulin sensitivity and had a beneficial effect on obesity, diabetes, and fatty liver disease [78, 79]. LECT2 is a novel hepatokine that mediates obesity and skeletal muscle IR [80]. Deletion of LECT2 in mice improved IR by phosphorylation of c-Jun N-terminal kinase (JNK) pathway in the skeletal muscle. The results of our study showed that the circulating LECT2 levels were higher in patients with NAFLD than in those without NAFLD [81]. Furthermore, LECT2 was positively associated with obesity, lipid profiles, hs-CRP, and liver aminotransferase levels. Hepatocyte-derived fibrinogen-related protein (HPS) is a protein involved in hepatic regeneration [82]. HPS can mediate IR and T2DM. Plasma HPS concentrations were upregulated in NAFLD by inducing hepatic steatosis through the extracellular signal-regulated kinase 1/2-dependent pathway [83]. Furthermore, HPS was independently correlated with fasting plasma glucose level, IR, impaired fasting glucose, impaired glucose tolerance, and newly detected diabetes in human [84]. In a recent study, increased HPS levels in hepatocytes caused IR in the skeletal muscle through epidermal growth factor receptor/JNK pathway [85].

Myokines

The skeletal muscle is an endocrine organ secreting myokines that regulate systemic metabolism. Irisin is a myokine which stimulates uncoupling protein-1, browning of adipose tissue and improves glucose intolerance and energy expenditure [86]. In the experimental models, irisin, in an AMPK-dependent manner, improves hepatic steatosis and glucose metabolism. In biopsy-proven NAFLD subjects, irisin levels were similar in NAFL and NASH; however, they were positively associated with the presence of portal inflammation [87]. Irisin levels were inversely related to hepatic triglyceride levels in 296 obese Chinese subjects [88]. These metabolic effects may be related to sarcopenia, but previous studies have shown contradicting results. We observed that circulating irisin levels were not different in subjects with sarcopenia compared with the controls using two different irisin enzyme-linked immunosorbent assay kits [89]. However, another study showed that irisin levels were positively correlated with ASM/height^2 and hand grip strength [90]. Myostatin, a member of the transforming growth factor superfamily, is predominantly released by the skeletal muscle and has a negative effect on the skeletal muscle [91]. Blocking myostatin increases muscle mass, improves insulin sensitivity and protects hepatic steatosis in mice [92].

Physical inactivity

Physical inactivity causes loss of muscle mass and excess positive energy balance aggravates obesity. Consequently, sarcopenia and NAFLD can be provoked and aggravated by chronic inflammation, IR, and oxidative stress. Exercise can increase muscle insulin sensitization, promote muscle protein synthesis, and myokine secretion. Physical activity reduces the risk of developing sarcopenia (OR 0.45; 95% CI 0.37–0.55) as revealed in a meta-analysis [93]. Exercise can improve metabolic health independent of weight loss [94]. After a 4-week aerobic cycling exercise, the hepatic triglyceride concentration was observed to be decreased by 21%.

Areas for future study

Several studies have investigated the role of genetics in the field of sarcopenia and NAFLD. The most extensively studied polymorphisms in sarcopenia are those of angiotensin converting enzyme (ACE) gene I/D, α-actinin-3 (ACTN3), and myostatin (MSTN) [95]. In a recent study in UK, variation in the human leukocyte antigen complex and noncoding single nucleotide polymorphisms was associated with sarcopenia [96]. However, whether the influence of genetic variations is direct or specific to muscle phenotypes or strength is controversial. In NAFLD, genetic variability

in patatin-like phospholipase domain-containing protein 3 (PNPLA3), transmembrane 6 superfamily 2 human gene (TM6SF2), membrane-bound O-acyltransferase domain-containing protein 7 (MBOAT7), and glucokinase regulatory protein (GCKR) genes was validated as a modifier [97]. Interestingly, there have been several studies that NAFLD/NASH and insulin resistance has been associated with genetic variation, such as PNPLA3. PNPLA3 I148 M variant is associated with high liver fat, but not with insulin sensitivity [98]. However, PNPLA3 I148 M allele was associated with insulin resistance in severely obese individuals [99]. Sarcopenia and NAFLD share common pathophysiology. Further studies on the elucidation of genetic aspects that mediates sarcopenia and NAFLD are needed.

Summary and conclusion

An increasing body of evidence indicates that sarcopenia may play a role in NAFLD, not only in the pathogenesis but also severity and prognosis. The underlying mechanisms for the pathophysiology of NAFLD are IR, obesity, low-grade inflammation, Vit. D deficiency, physical inactivity, hepatokines, and myokines. Interventions such as weight reduction, exercise, Vit. D supplementation, myostatin inhibitor administration, and insulin sensitizer therapy can be utilized to ameliorate the loss of muscle mass and improve hepatic steatosis (Fig. 3). High fructose diet is a well-known risk factor for NAFLD. The high fructose intake increases uric acid level thereby inducing insulin resistance and oxidative stress [100]. Thus, changing diet habit may be helpful in the management of sarcopenia as well as NAFLD. Aging and underlying diseases can contribute to the incidence of sarcopenia; NAFLD may be a risk factor for sarcopenia. Therefore, it is currently unclear if sarcopenia contributes to NAFLD or vice versa. Sarcopenia is a progressive loss of skeletal muscle mass, strength, and physical performance. Recent consensus suggests muscle function as a primary determinant in addressing sarcopenia. Considering the
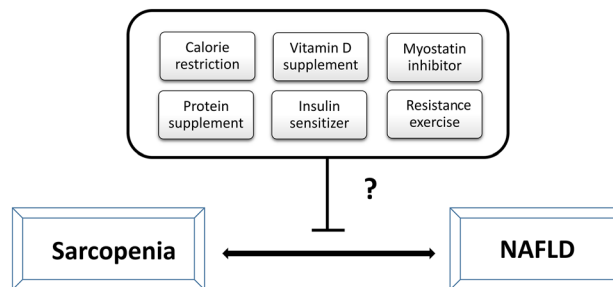
Fig. 3 Possible interventions to improve sarcopenia in NAFLD. *NAFLD* non-alcoholic fatty liver disease

clinical studies demonstrating the association of low muscle mass and NAFLD, further mechanistic studies on the effect of low muscle function/performance on NAFLD are necessary.

Compliance with ethical standards

Conflict of interest Jung A. Kim and Kyung Mook Choi have no conflicts of interest to disclose.

Ethical approval This article does not contain any studies with human or animal subjects.

Informed consent Informed consent is not required.

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