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Metabolic-associated Fatty Liver Disease and Sarcopenia: A Double Whammy

Metabolic-associated Fatty Liver Disease and Sarcopenia

Abstract

The prevalence of metabolic-associated fatty liver disease (MAFLD) has increased substantially in recent years because of the global obesity pandemic. MAFLD, now recognized as the number one cause of chronic liver disease in the world, not only increases liver-related morbidity and mortality among sufferers but also worsens the complications associated with other comorbid conditions such as cardiovascular disease (CVD), type 2 diabetes mellitus (T2DM), obstructive sleep apnoea (OSA), lipid disorders and sarcopenia. Understanding the interplay between MAFLD and these comorbidities is important to design optimal therapeutic strategies. Sarcopenia can be either part of the disease process that results in MAFLD (e.g., obesity or adiposity) or a consequence of MAFLD, especially in the advanced stages such as fibrosis and cirrhosis. Sarcopenia can also worsen MAFLD by reducing exercise capacity and by the production of various muscle-related chemical factors. Therefore, it is crucial to thoroughly understand how we deal with these diseases, especially when they coexist. We explore the pathobiological interlinks between MAFLD and sarcopenia in this comprehensive clinical update review article and propose evidence-based therapeutic strategies to enhance patient care.

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Core Tip: Metabolic-associated fatty liver disease (MAFLD) is associated with sarcopenia in a significant proportion of individuals. Sarcopenia can be a consequence of the comorbidities associated with MAFLD (such as obesity or adiposity) or a direct result of advanced stages of MAFLD such as fibrosis and cirrhosis. On the other hand, sarcopenia can worsen MAFLD due to reduced exercise capacity and the release of various myokines. Understanding the strong interlink between MAFLD and sarcopenia is important to plan appropriate therapeutic strategies. We discuss the pathobiological aspects of this interlink and the potential clinical and metabolic complications of the coexistence of MAFLD and sarcopenia in this comprehensive clinical update review.

INTRODUCTION

Metabolic-associated fatty liver disease (MAFLD) and sarcopenia are two chronic health conditions with profound adverse implications in modern society. MAFLD encompasses a spectrum of liver conditions, ranging from simple steatosis (fatty liver) to non-alcoholic steatohepatitis which involves inflammation and liver cell damage, advanced liver fibrosis, cirrhosis, and hepatocellular carcinoma (HCC). On the other hand, sarcopenia represents the progressive loss of muscle mass, strength, and function associated with aging, sedentarism, obesity, and conditions that cause reduced mobility. These two conditions have gained considerable attention due to their parallel rise in prevalence and potential interconnections. MAFLD is currently the most common liver disorder worldwide, affecting nearly one-third of the global population[1]. The definition and diagnostic criteria for sarcopenia have evolved in recent years. The European Working Group on Sarcopenia in Older People (EWGSOP) and the Asian Working Group for Sarcopenia (AWGS) have proposed consensus definitions that consider muscle mass, muscle strength, and physical performance measures[2,3]. Recent studies have highlighted the association between sarcopenia and various chronic diseases, including

cardiovascular disease, diabetes mellitus, and liver disease, emphasizing the importance of early detection and intervention[4,5]. MAFLD and sarcopenia are two interrelated conditions that pose significant challenges in clinical practice.

The intricate link between MAFLD and sarcopenia involves shared mechanisms, such as chronic low-grade inflammation, oxidative stress, insulin resistance, and alterations in adipokines and myokines[6,7]. MAFLD contributes to sarcopenia through negative impacts on muscle protein synthesis and metabolism, leading to wasting. Conversely, sarcopenia exacerbates MAFLD by influencing insulin resistance, dyslipidaemias, and systemic inflammation, and promoting liver fat accumulation through physical inactivity, weight gain, and central obesity[8,9]. The cumulative effect creates a cycle that worsens health outcomes and highlights the complex interplay between metabolic, inflammatory, and hormonal factors.

The clinical association between MAFLD and sarcopenia has important implications for patient management and outcomes. Understanding this association is crucial for identifying patients at high risk and implementing appropriate interventions to mitigate the disease progression. Recognizing and addressing these conditions early in clinical practice can help to improve patient prognosis and overall well-being. This review aims to explore the relationship between MAFLD and sarcopenia, shedding light on underlying mechanisms, common risk factors, potential consequences, and possible interventions.

The bidirectional relationship between MAFLD and Sarcopenia

Central to understanding mechanisms between MAFLD and sarcopenia is the concept of myosteatosis, which represents the infiltration of fat into skeletal muscle, contributing to functional decline as well as the loss of skeletal muscle mass seen in sarcopenia. Myosteatosis is seen in both Non-Alcoholic Steatohepatitis (NASH) as well as MAFLD. It may be a superior indicator and predictor of hepatocellular deterioration compared to sarcopenia, especially in the early stages of NASH, since it precedes the onset of sarcopenia[10,11]. Additionally, Myosteatosis has a strong association with liver stiffness

in obese patients with MAFLD[12], highlighting its role in the dynamic relationship between sarcopenia and MAFLD.

Numerous shared risk factors augment the bidirectional relationship between MAFLD and sarcopenia, acting as a precipitator of metabolic dysregulation. Factors include the male gender, physical inactivity, metabolic syndrome, older age, and raised total cholesterol, high-density lipoprotein (HDL) cholesterol, and low-density lipoprotein (LDL) cholesterol. Additionally, factors such as alcohol consumption, diabetes mellitus leading to elevated glycated haemoglobin (HbA1c) levels, and other co-morbidities contribute to the bidirectional risk[13-16]. Tables 1 and 2 provide an overview of studies illustrating both sarcopenia as a risk factor for MAFLD and Vice versa.

Table legends

BIA, Bioimpedance analysis; CAP, Controlled attenuation parameter; DXA, Dual-energy X-ray absorptiometry; LMM, Low muscle mass; LMS, Low muscle strength; LUTE, Liver ultrasound transient elastography; MAFLD, Metabolic-associated fatty liver disease; NAFLD, Non-alcoholic fatty liver disease; US, Ultrasonography.

These tables are adapted and updated form of the work from **Joo SK, Kim W. Interaction between sarcopenia and nonalcoholic fatty liver disease. Clin Mol Hepatol. 2023 Feb;29(Suppl):S68-S78. Copyright © 2023 by The Korean Association for the Study of the Liver** [28].

Pathogenic pathways in the liver-muscle axis

The intricate relationship between MAFLD and sarcopenia is characterised by shared pathogenic mechanisms, complicating efforts to identify a primary instigator. Central to this is insulin resistance, a pivotal factor in influencing both metabolic and growth processes. Physiologically, insulin plays a key role in lowering blood glucose and fatty acid levels through the suppression of adipose tissue lipolysis and hepatic glucose output[29]. It also increases glucose uptake into adipose and muscle tissue through phosphorylation of insulin receptor substrate (IRS) and subsequent exocytosis *via* glucose transporter type 4 (GLUT 4)[30]. Additionally, insulin plays a role in muscle protein synthesis, mediated *via* key signalling pathways such as Akt/protein kinase B and

mammalian target of rapamycin (mTOR)[31]. Insulin resistance (IR) in adipose and muscle tissue therefore contributes significantly to the clinical progression of both MAFLD and sarcopenia. IR has strong associations with obesity and metabolic syndrome as well as its association with low muscle mass due to age-related degeneration, as seen in sarcopenia. Adipose tissue IR leads to heightened release of free fatty acids (FFAs), prominently observed in MAFLD patients[32], contributing to liver triglyceride accumulation, and fostering a pro-inflammatory environment[33,34].

MAFLD is associated with low levels of growth Hormone (GH) and insulin-like growth factor (IGF-1), contributing to increased hepatic IR and body adiposity. GH is crucial in increasing beta-oxidation of FFAs, potentially ameliorating hepatic lipid content, whilst IGF-1 exerts anti-inflammatory and anti-fibrotic effects in the liver[35]. Hormonal changes, particularly in post-menopausal women and individuals with altered testosterone levels, further complicate this relationship. The prevalence of sarcopenia is high amongst post-menopausal women[36], with menopausal hormonal therapy (MHT) demonstrating a possible protective effect[37]. Testosterone is essential for muscle regeneration in males, and its deficiency contributes to reduced lean muscle mass in sarcopenia. Additionally, this deficiency may coincide with obesity and culminate in a pro-inflammatory state through the release of mediators such as IL-6 and TNF-α[38,39,40], thereby worsening sarcopenia and steatohepatitis.

In MAFLD, inflammation is further intensified by lipotoxicity, leading to increased reactive oxygen species and oxidative stress. This cascade results in intrahepatic cellular damage and higher circulating levels of FFAs within the cytosol[41,42]. Myokines, signalling molecules produced by skeletal muscle, play a role in energy metabolism. Sarcopenic MAFLD individuals show reduced levels of myokines, attributed to muscle loss and lack of physical activity[43]. Irisin, an exercise-induced myokine, demonstrates a protective effect against fatty liver[44] and shows a positive relationship with Fibroblast growth factor 21 (FGF-21) in animal studies, suggesting its potential therapeutic effects of reversing hepatic steatosis[45,46].

Figure 1. depicts the pathways contributing to the progression of both liver and muscle dysfunction in MAFLD and sarcopenia.

Clinical evidence linking MAFLD and Sarcopenia

The relationship between fatty liver disease (formerly NAFLD, now MAFLD) and sarcopenic muscle degeneration has been extensively explored in numerous studies, though variations in selection criteria exist due to the recent redefinition of the disease. The shift to MAFLD has broadened the identification of individuals with liver disease.

Between 2018-19, four meta-analyses investigated the link between NAFLD and sarcopenia, with one study exploring the progression of fatty liver disease also. One meta-analysis reported a significantly increased risk of NAFLD in patients with sarcopenia (pooled Odds Ratio -OR- of 1.54), emphasising a substantial association despite there being statistical heterogeneity[47]. Another meta-analysis confirmed this increased risk of both NAFLD and a heightened risk of significant fibrosis[48]. In concordance with these results, a strong association was found between sarcopenia and advanced liver disease, with an odds ratio of 2.41[49]. Cai *et al*'s[50] meta-analysis involving 19 studies, further reported higher risks of NAFLD, NASH, and significant fibrosis in individuals with reduced skeletal mass.

Diagnostic variation between studies is evident as there are no standardized diagnostic criteria to measure skeletal muscle mass and fat in the liver. Diagnostic CT/MRI are superior modalities for skeletal mass measurement however, they pose a challenge in larger study settings. Dual-energy X-ray absorptiometry (DXA) is a preferred tool for its ease of use, but there are limitations in estimating lean mass and quantifying intramuscular adiposity, especially in cases of myosteatosis[51].

Recent studies, focusing on MAFLD as opposed to NAFLD, provide a pragmatic clinical evaluation accounting for metabolically deranged individuals. A large study involving 8,371 patients revealed increased risks of significant liver fibrosis and atherosclerotic cardiovascular disease in those with both MALFD and sarcopenia. Sarcopenic individuals with MAFLD exhibited higher odds ratios for significant fibrosis (Fibrosis 4 Index: Odds Ratio - 4.51, NAFLD Fibrosis Score: Odds Ratio - 5.72) and cardiovascular

disease (Odds Ratio (OR) 4.08) compared to non-sarcopenic counterparts[52]. Another investigation involving 6,424 subjects, using Fibro scan and bioimpedance analysis (BIA), found an association between MAFLD and increased risk of low muscle mass adjusted for weight and BMI, with the diabetic MAFLD subgroup showing the highest risk[53]. Notably a reverse relationship was found between appendicular skeletal muscle mass (ASM) and the risk of MAFLD across both sexes, with appendicular skeletal mass of the highest quartile being associated with the least risk of MAFLD[54].

Lean MAFLD and Sarcopenia

Lean MAFLD poses a challenge to clinicians as fatty liver disease presents in individuals with a lower BMI and adipose tissue and contradicts the criteria of MAFLD, which is usually associated with metabolic syndrome and obesity[55]. A United States-based population study found the prevalence of NAFLD to be 4 per 100,000 and lean NAFLD to be 0.6 per 100,000, where patients with lean NAFLD tended to be older, females, smokers, and of Asian race[56]. Global estimation of lean NAFLD was around 4.1%, with Asian populations having the highest prevalence (4.8%)[57]. Jane Ha, *et al*'s[58] investigation revealed that lean MAFLD individuals faced a relative risk of 1.12 for cardiovascular mortality and 1.88 for liver-related mortality compared to non-lean individuals. However, varied findings from a Chinese cohort study indicate that, while obese NAFLD individuals have a higher CVD risk, lean NAFLD individuals still face elevated risks of all-cause death, digestive system cancers, and obesity-related cancers[59]. Despite having milder features of metabolic syndrome, lean individuals have been shown to have a higher prevalence of metabolic abnormalities such as dyslipidaemia, hypertension, insulin resistance, and diabetes mellitus[60]. Sarcopenic patients have shown upregulated serum levels of N-acetylneuraminyl-glycoproteins, lactic acid, LDL triglycerides, and VLDL5 Levels, along with reduced HDL4 Levels[61]. A study by Nabi *et al*[62] confirmed patients with lean NAFLD were associated with advanced liver fibrosis (OR = 1.26) compared to non-lean individuals, highlighting the necessity to re-evaluate assumptions about the health of lean individuals. The optimisation in skeletal muscle

mass, as opposed to the sole reduction in visceral adiposity, has been suggested for optimal management of lean MAFLD[63].

Sarcopenic-obesity and MAFLD

Sarcopenic obesity (SO), being the co-existence of loss of muscle mass alongside increased body adiposity/fat mass, is a prevalent condition affecting 11% of older adults globally[64]. In males, identified risk factors include increased body mass index (BMI), waist circumference, and triglyceride levels, along with a decreased skeletal muscle mass index. For females, height, weight, BMI, waist circumference, and systolic blood pressure, as well as smoking status and fasting glucose are identified as significant risk factors, according to a large nationwide Korean study[65].

The pathophysiology of sarcopenic obesity can be attributed to a multitude of mechanisms such as aging, insulin resistance, low-grade inflammation, and hormonal changes[66]. Aging induces a progressive loss in muscle mass and an increase in adiposity due to a decline in basal metabolic rate, inactivity, and hormonal fluctuation. The increased visceral fat and net loss of muscle mass, coupled with aging can encourage a reduction in GH production[67], negatively impact protein synthesis, and exacerbate sarcopenia.

Diagnosis, as detailed by the European Society for Clinical Nutrition and Metabolism (ESPEN)[68], involves screening for high BMI and waist circumference, using surrogate indicators for sarcopenia with diagnostic cut-offs based on ethnicity, age, and gender. Functional assessments, including muscle strength evaluation and body composition analysis based on DXA, BIA, and CT, are used to finalize the diagnosis. Advanced liver disease warrants the use of CT/ MRI imaging for accuracy, due to its ability to effectively eliminate the confounding effects of fluid retention, particularly ascites, and oedema, associated with portal hypertension[69].

Sarcopenic obesity has been shown to increase the risk of all-cause mortality, and fragility fractures in elderly patients with type 2 diabetes mellitus[70,71]. Low muscle-to-fat ratio in older adults has been linked to impaired health outcomes and increased cardiometabolic and cardiovascular risk[72,73]. SO is also associated with a significant increase in the risk

of coronary artery calcification[74]. In children, sarcopenic obesity is linked to the development of metabolic syndrome and worsened outcomes in type 2 diabetes mellitus[75].

Moreover, sarcopenic obesity also increases the risk of MAFLD development and fibrosis progression[76]. Increased visceral adiposity and insulin resistance, resulting in hepatic fat accumulation[77], contribute to worsened hepatic fibrosis, as demonstrated by Kim *et al*[78]. Understanding the relationship between sarcopenic obesity and these health outcomes is crucial for holistic patient care.

Clinical complications and their significance

In MAFLD, the presence of sarcopenia worsens disease progression and outcomes. Reduced muscle mass leads to physical inactivity, which can exacerbate metabolic dysfunction, insulin resistance, and the accumulation of visceral adiposity[79]. Inflammation in the liver is further aggravated by the sarcopenia-associated cytokine and adipokine profiles. Conversely, MAFLD can contribute to the development of sarcopenia through chronic inflammation, leading to muscle breakdown.

Insulin Resistance (IR) resulting from MAFLD impairs glucose uptake into the muscle, and metabolic alterations in MAFLD can lead to increased oxidant stress in muscle tissue. IR, a common feature in MAFLD, sarcopenia, and diabetes mellitus, worsens glycaemic control, inflammation, and metabolic dysfunction, thereby escalating the risk of cardiovascular disease. Notably, the presence of sarcopenia in diabetes mellitus increases the risk of all-cause mortality and cardiovascular mortality[80]. Studies, such as the post-hoc analysis of the ATTICA study, detailed that a lower skeletal muscle percentage is associated with an increased risk of MAFLD, with a substantial rise in cardiovascular risk when sarcopenia exists, irrespective of waist circumference [81,82]. These disease outcomes were also reaffirmed in a study of 11,065 Sarcopenic MAFLD patients, who faced a 28% higher likelihood of all-cause mortality, all with elevated risk of cancer and diabetes-related mortality[83].

A further study of 852 diabetic participants demonstrated a higher risk of carotid atherosclerotic progression over a 6–8-year span in those with both sarcopenia and

MAFLD (or 2.2)[84]. Albuminuria, a marker of renal dysfunction and cardiovascular risk, was also shown to have significantly higher rates in patients with both conditions[85]. Moreover, the progression of fibrosis in the presence of sarcopenia has been extensively studied. In a recent study of 2422, sarcopenic NAFLD demonstrated higher liver fibrosis rates than NAFLD alone. Rates of Significant fibrosis were elevated (18.3% *vs* 3.2%) and a similar marked increase was seen in advanced fibrosis[86]. The interplay between the two conditions has been shown to worsen surgical outcomes and long-term post-operative survival of hepatocellular carcinoma (HCC) patients with MAFLD[87]. Sarcopenia was identified as an independent risk factor for both recurrence-free survival and overall survival in sarcopenic MAFLD patients with HCC. Additionally, sarcopenia in MAFLD is associated with higher rates of depression and fatigue, along with a reduced quality of life[88].

The synergy of both conditions leads to increased metabolic dysregulation, contributing to a more adverse clinical course of MAFLD, emphasising the need for a comprehensive assessment to address the multiple implications of having both sarcopenia and MAFLD. Figure 2 illustrates the clinical implications of sarcopenia and MAFLD, as discussed prior.

Figure. 2 Clinical complications associated with MAFLD and sarcopenia. Original image created for use in this review.

Clinical management of MAFLD with Sarcopenia

A multifaceted approach must be used to address the combination of Metabolic-associated Fatty liver disease (MAFLD) and sarcopenia. Conservative management of MAFLD involves gradual weight loss and regular physical activity, both of which improve hepatic steatosis and quality of life[89,90], as well as improving liver stiffness[91]. Aerobic and resistance training, especially moderate resistance training, was found to be beneficial in ameliorating insulin resistance[92]. Bariatric surgery may be offered for individuals with BMI >40 kg/m^2 and obesity-related comorbidities, with the exclusion of those with decompensated cirrhosis and concomitant portal hypertension[93].

When managing sarcopenia, a meta-analysis highlights the effectiveness of nutritional supplementation and physical activity for outcomes such as muscle mass, strength, and physical performance[94]. Strength training induces muscle hypertrophy and mitigates the decline in lean muscle tissue[95]. Although physical activity has been shown protective effects against both conditions[96], its utility is limited due to the heightened frailty seen in the advanced stages of these diseases[97]. Evaluation of sarcopenia through imaging and muscle strength assessment is crucial, before commencing treatment. Whilst protein supplementation alone may not be useful for sarcopenia[98], branched-chain amino acids (BCAAs) show promise, especially in sarcopenic patients with Cirrhosis[99].

The implication of diet in sarcopenia and MAFLD remains an area for exploration, although it is a smaller prognostic factor in patients with sarcopenic MAFLD compared to physical activity[100]. Pharmacological treatment often targets pre-existing co-morbidities such as cardiovascular disease, diabetes mellitus, and lipid abnormality, focusing on regulating the patients' metabolic status. For example, Vitamin E supplementation demonstrates significant improvements in ALT/AST, fibrosis, and steatosis for patients with MAFLD, with a notable reduction in fibrosis score[101]. A meta-analysis has shown the use of GLP–1 analogue leads to notable enhancements in liver enzymes, liver fat content, HbA1c, and weight in individuals with both type 2 diabetes mellitus and MAFLD[102]. Whilst thiazolidinediones have shown efficacy in MAFLD treatment, GLP-1 analogues appear to be superior[103]. SGLT2 inhibitors also demonstrate similar efficacy to thiazolidines, with the added benefit of weight reduction[104]. Statins have anti-inflammatory properties, and their use has further been associated with a lower prevalence of NASH and fibrosis, highlighting their protective role against the progression of MAFLD[105]. As seen, a comprehensive approach to managing MAFLD and sarcopenia involves lifestyle interventions, targeted pharmacotherapy, and ongoing research for optimal care.

Areas of uncertainty/ Emerging research questions

Emerging pharmacological interventions aim to target inflammatory and fibrotic pathways in fatty liver disease. A review by A Rojas *et al*[106] outlines therapies in phase

II/III clinical trials, which focus on reducing fatty acid accumulation and regressing fibrosis.

Novel mechanisms have been researched to explain the pathogenesis of both conditions, as well as to unravel their bidirectional nature. A recent study was done on the involvement of the phosphoenolpyruvate carboxykinase 1 (PCK1) enzyme in MAFLD and NASH progression[107]. This study aimed to investigate the role of PCK1, a gluconeogenic enzyme, in the promotion of MAFLD through the study of rodents. It was found that PCK1 was downregulated in NASH patients and rodents with MAFLD. A further study by Xu, *et al*[108] investigated transcription pattern mapping to identify the core genes and possible therapeutic targets that regulate MAFLD and sarcopenia, revealing 8 shared genes with common pathways.

Another area of interest is the impact of aging and associated low-grade inflammation on metabolic-associated diseases. As opposed to Metaflammation, which is the inflammation present under overnutrition and metabolic disease, Inflammaging is a relatively new term that describes a low-grade inflammation that arises through aging[109]. Its mechanism is not fully understood; however, it is a common factor in the development of both sarcopenia and MAFLD[110]. Future research may be directed at not only understanding these mechanisms but also developing targeted therapeutics to reverse such pathological outcomes.

CONCLUSION

Understanding the clinical association between MAFLD and sarcopenia is crucial for a comprehensive approach to patient care. By recognizing the bidirectional relationship, shared risk factors, and impact on various outcomes, healthcare providers can implement targeted interventions, promote early detection, and optimize treatment strategies for individuals affected by these conditions. Further research is needed to unravel the complex mechanisms, explore targeted interventions, and develop personalized treatment strategies for individuals with this complex clinical association.

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