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EDITORIAL

The bidirectional relationship between nonalcoholic fatty liver disease and sarcopenia

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Abbreviations

ASM	Appendicular skeletal muscle
BMI	Body mass index
HGS	Handgrip strength
LMM	Low muscle mass
LMS	Low muscle strength
NAFLD	Nonalcoholic fatty liver disease

The global epidemic of obesity and metabolic syndrome in an aging population have led to an increased prevalence of many chronic conditions including nonalcoholic fatty liver disease (NAFLD), the hepatic manifestation of metabolic syndrome, and sarcopenia, defined as generalized loss of skeletal muscle mass and/or function. While these conditions may seem, at first, to be independent of each other, there is a growing body of literature examining the role of sarcopenia on the development and progression of NAFLD. Prior studies have shown a five-fold increased risk of NAFLD in patients with sarcopenia [1] with subsequent studies demonstrating a two to three-fold increased risk of nonalcoholic steatohepatitis and advanced fibrosis in patients with sarcopenia independent of obesity, insulin resistance, inflammation, and metabolic syndrome [2–4]. Limited data from longitudinal studies have supported these cross-sectional observations, which demonstrated a decreased incidence and resolution of existing NAFLD in patients with increased skeletal muscle mass after adjusting for several known risk factors [5]. Although these studies demonstrated a *relationship* between NAFLD and sarcopenia, there has been insufficient evidence to support a direct *causal* relationship between these two entities beyond their shared association with the metabolic syndrome. Thus, it is challenging to determine whether sarcopenia is a risk factor for disease progression of NAFLD, or a complication of NAFLD due to worsening liver disease.

In this issue of *Hepatology International*, Roh and colleagues leveraged data from a large nationwide multicenter longitudinal database, the Korean Frailty and Aging Cohort, to begin to address this gap [6]. They investigated the impact of NAFLD on the longitudinal risk of sarcopenia in a large cohort of elderly community-dwelling participants in Korea with at least 2 years of follow-up. NAFLD was defined as the presence of hepatic steatosis using several non-invasive scores including hepatic steatosis index, fatty liver index, and NAFLD liver fat score. Handgrip strength (HGS) was measured using digital hand grip dynamometer of the dominant arm, and appendicular skeletal muscle (ASM) was measured using dual-energy x-ray absorptiometry scan; both metrics were adjusted by body mass index (BMI). Low muscle mass (LMM) and low muscle strength (LMS) were categorized using sex-specific lowest quintiles of ASM/BMI and HGS/BMI, respectively. The key finding of this study was the strong association between hepatic steatosis and the *subsequent* development of LMM and LMS in older adults at 2 years of follow-up. This association was observed even after adjustment for age, sex, lifestyle factors including physical activity, comorbidities, and other risk factors such as insulin resistance and systemic inflammation. Notably, there was no observed association between advanced fibrosis (defined as BARD score > 2) and development of LMM or LMS after 2 years, despite prior studies [2, 4] demonstrating a significant association between sarcopenia and advanced fibrosis [based on other non-invasive scores (NAFLD fibrosis score, FIB-4, and Forns index) [4] or histology [2]]. Lastly, it is worth noting that cutoffs for both LMM and LMS were based on BMI. BMI does not account for differential body composition, which is particularly important for older adults as aging is characterized by both an increase in total body fat mass and decrease in skeletal muscle mass.

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Thus, both LMM and LMS may be lower than indicated and may be overestimated in this study. As sarcopenia is considered an age-related process, it would have been interesting to include older adults without NAFLD as a comparison group. Nonetheless, the rigorous analyses of this unique and large population dataset with longitudinal follow-up further demonstrates the interconnected bidirectional relationship between NAFLD and sarcopenia.

Although these data do not allow us to explore the mechanism of this relationship, we offer a possible explanation. NAFLD and sarcopenia share a pathophysiological pathway along the muscle-liver-adipose axis. This crosstalk between muscle, liver, and adipose tissue is influenced by several factors including obesity, different adipose tissue depots, insulin resistance, and chronic low-grade inflammation, along with mediators such as aging, physical inactivity, unhealthy diet, vitamin D deficiency and hormonal imbalance (i.e., growth hormone, insulin-growth factor 1, testosterone) [7, 8]. Loss of skeletal muscle is associated with insulin-resistance resulting in decreased glycogenesis and increased adipose tissue lipolysis, further accelerating proteolysis. Furthermore, the accumulation of visceral adipose tissue is associated with chronic low-grade inflammation mediated by adipokines and proinflammatory cytokines, leading to increased liver inflammation and fibrosis [9]. Additionally, altered level of myokines from decreased skeletal muscle mass can lead to hepatic fat accumulation. These dysregulations potentiate further hepatocytes injury through increased inflammation, lipotoxicity, mitochondrial dysfunction, oxidative/endoplasmic reticulum stress, and anabolic resistance, further contributing to disease progression [8]. Thus, interventions that can impact muscle composition while simultaneously involving multiple pathways within the muscle-liver-adipose axis are needed to address the multifactorial pathogenesis of NAFLD and sarcopenia.

This work by Roh and colleagues is all the more important in the context of increasing recognition of sarcopenic obesity as a distinct phenotype, defined as the state of decreased muscle mass in the setting of increased fat mass [10], among patients with NAFLD, not to mention cirrhosis in general. Sarcopenia is a clear determinant of non-liver and liver-related morbidity and mortality including hepatic decompensation, prolonged hospitalization, and reduced quality of life [10]. Thus, awareness of different clinical phenotypes of NAFLD (e.g., sarcopenic obesity) would allow for better stratification of individuals at higher risk for disease progression for more individualized management strategies with weight loss while preserving skeletal muscle mass and/or function. The preservation of muscle mass would in turn promote release of favorable myokines and subsequently decrease hepatic fat accumulation/inflammation and improve negative long-term NAFLD-related outcomes. An emerging non-invasive method for characterizing body composition (e.g., visceral adipose tissue, subcutaneous adipose tissue, and skeletal muscle) is cross-sectional imaging with computed tomography, as it would allow for more objective evaluation of nutritional and metabolic status, in addition to identifying different clinical phenotypes of NAFLD for a targeted therapy approach. Clearly, further studies are needed to determine the benefit of sarcopenic management on improvement of NAFLD-related outcomes, and vice versa.

Overall, the present study adds valuable information to the existing literature on NAFLD and sarcopenia, in particularly the impact of hepatic steatosis on the risk of sarcopenia via loss of skeletal muscle mass and reduced function. Although the exact mechanism linking NAFLD with sarcopenia and sarcopenic obesity is not fully understood, the shared pathophysiologic pathways offer a possible therapeutic strategy targeting NAFLD while simultaneously preserving muscle mass.

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Declarations

Conflict of interest The authors (Nghiem B. Ha and Jennifer C. Lai) declare that they have no conflict of interest.

References

1. Hong HC, Hwang SY, Choi HY, Yoo HJ, Seo JA, Kim SG, et al. Relationship between sarcopenia and nonalcoholic fatty liver disease: the Korean Sarcopenic Obesity Study. Hepatology. 2014;59:1772–1778
2. Koo BK, Kim D, Joo SK, Kim JH, Chang MS, Kim BG, et al. Sarcopenia is an independent risk factor for non-alcoholic steatohepatitis and significant fibrosis. J Hepatol. 2017;66:123–131
3. Lee YH, Jung KS, Kim SU, Yoon HJ, Yun YJ, Lee BW, et al. Sarcopaenia is associated with NAFLD independently of obesity and insulin resistance: nationwide surveys (KNHANES 2008–2011). J Hepatol. 2015;63:486–493
4. Lee YH, Kim SU, Song K, Park JY, Kim DY, Ahn SH, et al. Sarcopenia is associated with significant liver fibrosis independently of obesity and insulin resistance in nonalcoholic fatty liver disease: nationwide surveys (KNHANES 2008–2011). Hepatology. 2016;63:776–786
5. Kim G, Lee SE, Lee YB, Jun JE, Ahn J, Bae JC, et al. Relationship between relative skeletal muscle mass and nonalcoholic fatty liver disease: a 7-year longitudinal study. Hepatology. 2018;68:1755–1768
6. Roh E, Hwang SY, Yoo HJ, Baik SH, Lee JH, Son SJ, Kim HJ, et al. Impact of non-alcoholic fatty liver disease on the risk of sarcopenia: a nationwide multicenter prospective study. Hepatol Int 2021.

7. Bhanji RA, Narayanan P, Allen AM, Malhi H, Watt KD. Sarcopenia in hiding: the risk and consequence of underestimating muscle dysfunction in nonalcoholic steatohepatitis. Hepatology. 2017;66:2055–2065
8. Zambon Azevedo V, Silaghi CA, Maurel T, Silaghi H, Ratziu V, Pais R. Impact of sarcopenia on the severity of the liver damage in patients with non-alcoholic fatty liver disease. Front Nutr. 2021;8:774030
9. du Plessis J, van Pelt J, Korf H, Mathieu C, van der Schueren B, Lannoo M, et al. Association of adipose tissue inflammation with histologic severity of nonalcoholic fatty liver disease. Gastroenterology. 2015;149:635–648 (**e614**)
10. Lai JC, Tandon P, Bernal W, Tapper EB, Ekong U, Dasarathy S, et al. Malnutrition, frailty, and sarcopenia in patients with cirrhosis: 2021 practice guidance by the American Association for the Study of Liver Diseases. Hepatology. 2021;74:1611