



Skeletal muscle mass and sarcopenia in nonalcoholic fatty liver disease

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Nonalcoholic fatty liver disease (NAFLD) is currently the leading cause of chronic liver disease worldwide. One-fourth of the world population may have NAFLD, with higher prevalence in the Middle East and South America (1). In the US population, national estimates have shown that 80 million people were affected in 2015, with the prediction of more than 100 million patients in 2030 (2). In Asia, the prevalence of NAFLD is as high as North America, which is thought to be due to the introduction of the Western diet. NAFLD has wide ranges of disease spectrum from nonalcoholic fatty liver, nonalcoholic steatohepatitis (NASH), and liver fibrosis, which can progress to cirrhosis and hepatocellular carcinoma. NAFLD is significantly associated with obesity, type 2 diabetes, hyperlipidemia, hypertension, and metabolic syndrome (1).

Sarcopenia is an age-related loss of muscle mass with impaired muscle strength and function. This condition affects approximately one-tenth of the world population and is projected to increase shortly as the world has been entering the aging society (3). Mechanism of sarcopenia involves aging processes like alteration of hormones, insulin resistance, cellular dysfunction, physical inactivity, malnutrition, and neurodegenerative diseases (4).

There are several essential studies attempted to find an association between sarcopenia and NAFLD, NASH, and advanced fibrosis in NAFLD. A Korean study found an increased risk of NASH and advanced fibrosis in the sarcopenic group, adjusted odds ratio (OR) 2.30 [95%

confidence intervals (CI): 1.08–4.93) and adjusted OR 2.05 (95% CI: 1.01–4.16) respectively (5). A recent US population-based study showed a significant increase risk of NAFLD and advanced fibrosis after adjusted for metabolic risk factors and inflammatory markers, with adjusted OR 1.24 (95% CI: 1.03–1.48) for NAFLD and adjusted OR 1.79 (95% CI: 1.18–2.72) for advanced fibrosis (6). A recent longitudinal study in Korean population showed a benefit of increasing muscle mass in the incident and resolution of NAFLD, the adjusted hazard ratio (HR) 0.69 (95% CI: 0.59–0.82) for the incidence of NAFLD and adjusted HR 4.17 (95% CI: 1.90–6.17) for resolution of NAFLD (7). In terms of meta-analysis, a study by Wijarnpreecha *et al.* is the first paper to summarize all the published data (8). The result showed that sarcopenia increases the risk of NAFLD with a pooled OR 1.54 (95% CI: 1.05–2.26), though there was high heterogeneity between studies (8). Sarcopenia also associated with histological NASH and advanced fibrosis in NAFLD from a meta-analysis of three studies, OR 2.35 (95% CI: 1.45–3.81) and OR 2.41 (95% CI: 1.94–2.98), respectively (9).

A recent meta-analysis from Cai *et al.* investigated the association between two diseases in terms of skeletal muscle mass (SMM) (10). In this study, skeletal muscle index (SMI) was calculated from SMM, which were obtained from two widely-used standard methods, bioimpedance analysis, and dual-energy X-ray absorptiometry. However, due to the absence of clear definition and cut-off value

for the diagnosis of sarcopenia (11), SMM was adjusted with different parameters, including weight, height, and body mass index for calculation of SMI. But, in this meta-analysis, SMI was calculated based on adjusted SMM with bodyweight only, which eliminated the bias of different calculation methods. In this study, patients with NAFLD had low SMM compared to healthy control, with the weighted mean difference (WMD) of -1.77 (95% CI: -2.39 to 1.15). This result was consistent with the previous meta-analysis which showed an independent association between sarcopenia and NAFLD. However, there was still high heterogeneity between studies. In this study, subgroup analysis showed that women had lower WMD than men. This result is similar in a general population study, in which the prevalence of sarcopenia is equal among both genders, but the degree of sarcopenia tends to be more severe in women (12). There was an increased risk of NAFLD in sarcopenic population, with a pooled adjusted OR of 1.33 (95% CI: 1.20 – 1.48), which is concordance with previous studies. The Asian population had a 37% increased risk of NAFLD compared to the Caucasian population. In terms of the association between sarcopenia and NASH, there is a significant association with a pooled OR of 2.42 (95% CI: 1.27 – 3.57). The risk of significant fibrosis in sarcopenic patients has been determined with a pooled adjusted OR of 1.56 (95% CI: 1.34 – 1.78) without any heterogeneity among studies.

Currently, liver biopsy is the gold standard for the diagnosis of NASH and advanced fibrosis. The non-invasive method such as elastography has some limitations in obese patients and in mild to moderate fibrosis (13). Another non-invasive method included FIB-4 and NAFLD fibrosis score to assess advanced fibrosis. The sensitivity and specificity for NAFLD fibrosis score is 67% and 97%, while FIB-4 has a sensitivity of 34% and specificity of 98% (14). In this meta-analysis study, a subgroup analysis was performed based on different diagnostic methods of NAFLD (10). The result showed that there are higher odds for studies using invasive measures (liver biopsy) for diagnosing NAFLD-related fibrosis among sarcopenia patients (OR 2.05 , 95% CI: 1.20 – 2.90) compared for studies using the non-invasive measures such as NFS, FIB-4 score (OR 1.52 , 95% CI: 1.29 – 1.75) (10).

This meta-analysis searched for studies in major databases with well-constructed search terms that covered the topic. Studies included were mostly high quality in study design and method, but few studies have low to moderate quality, which might affect heterogeneity and

bias of the study. There was a high number of studies and study participants in the sarcopenia and NAFLD analytic group, which reflected the power of this meta-analysis, though there was some heterogeneity among the included studies. The diagnosis of sarcopenia is yet controversial due to variety in cut-off value and adjusted parameters which derived from the standard deviation of sex-specific mean skeletal mass in certain reference populations (12,15). Because only two published studies were included for the Caucasian population compared to ten studies for Asians, this result regarding the association between sarcopenia and NAFLD needs to interpret cautiously and there should be more study to determine the risk in this population. Though there is significant publication bias in the report regarding the association between sarcopenia and NASH, the author proved that the bias did not affect the outcome by using the trim-and-fill method. However, there was still the minimal impact of the bias on the result after the trim-and-fill analysis, when they analyzed the association between sarcopenia and advanced fibrosis. Therefore, a cautious interpretation of the results is needed.

Postulated mechanisms for the association between sarcopenia and NAFLD may be explained by systemic inflammatory response, insulin resistance, and obesity (16). Cytokines and inflammatory markers including IL-6, TNF- α , and CRP, are found in both patients with sarcopenia and NAFLD. These markers are contributed to the catabolic state of muscles, protein synthesis interference, and fat deposition in the liver (17). In addition, insulin resistance increases muscle protein breakdown and inhibits protein synthesis that contributes to muscle wasting and sarcopenia (18). Moreover, insulin resistance enhanced free fatty acid uptake and increased hepatic fat accumulation (19). Obesity is associated with sarcopenia and NAFLD due to the mechanism of insulin resistance and systemic inflammation modulated by adipokine production from adipose tissue (20).

Recently published studies, particularly from Asia, have shown similar outcomes of a relationship between sarcopenia and NAFLD, which affirms the result from this meta-analysis (21–23). Low handgrip strength as a proxy of muscle strength to define sarcopenia was significantly associated with NAFLD in men (OR 2.51 , 95% CI: 1.18 – 5.33), and women (OR 2.34 , 95% CI: 1.41 – 3.89), and was inversely correlated with hepatic steatosis index as a well-validated tool for NAFLD (24). However, a recent study from the Netherlands showed no association between sarcopenia and NAFLD in men, but the protective effect

of SMM on NAFLD in women (25). Therefore, the race/ethnicity might play some role in the association between two diseases.

Overall, this meta-analysis showed a comprehensive review of the association between SMM as a proxy of sarcopenia and NAFLD and significant fibrosis. There is a significantly increased risk of NAFLD and fibrosis in individuals with low muscle mass. In the future, more study is required to confirm the association in different ethnic groups and to understand more of pathophysiology between these two conditions.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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