Editorial

Impact of sarcopenia on the progression of nonalcoholic fatty liver disease: a frequently forgotten association

Andrew A. Li[1], Aijaz Ahmed[2], Donghee Kim[2]

[1]Department of Medicine, [2]Division of Gastroenterology and Hepatology, Stanford University School of Medicine, Stanford, CA, USA

Correspondence to: Donghee Kim, MD, PhD. Division of Gastroenterology and Hepatology, Stanford University School of Medicine, 300 Pasteur Drive, Stanford, CA 94304, USA. Email: messmd@chol.com.

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The development of sarcopenia in patients with chronic liver disease has been recognized as a predictor of poor outcome. Sarcopenia, or the progressive loss of skeletal muscle mass begins to manifest in the early stages of chronic liver disease and worsens with progression to advanced liver disease with a prevalence approaching 60% in patients with end-stage liver disease (1). Nonalcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease worldwide with a disease spectrum ranging from relatively static isolated nonalcoholic fatty liver (NAFL) to progressive nonalcoholic steatohepatitis (NASH), which can lead to advanced fibrosis and cirrhosis. Although a majority of patients with NASH are obese, not all individuals with obesity develop NASH (2). Furthermore, NASH has been diagnosed with a relatively lower frequency in non-obese individuals (2). Recent cross-sectional studies have linked sarcopenia with both NAFLD and NASH as well as significant fibrosis beyond what is explained by obesity (3-6), though the cross-sectional design of these studies precludes a conclusion of temporal association. The interaction between muscle homeostasis and NAFLD is an intriguing concept due to the role of skeletal muscle in energy metabolism. Koo *et al.* reported an increasing prevalence of sarcopenia with the progression from without NAFLD (8.7%) to NAFLD (17.9%), and then to NASH (35%) (4). In addition, sarcopenia was associated with greater degrees of steatosis and fibrosis, with 46% of individuals with sarcopenia having significant fibrosis compared to 25% of those without sarcopenia (4). Sarcopenia was associated with a 2.5-fold higher risk of NASH and significant fibrosis in those with NAFLD, independent of obesity and insulin resistance (4). Limited longitudinal data have supported the cross-sectional observations. More recently, Kim *et al.* reported a 7-year longitudinal cohort study examining the relationship between skeletal muscle mass and NAFLD defined by hepatic steatosis index (7). Approximately, 15% of subjects without NAFLD at baseline developed incident NAFLD during the 7-year observation, with the highest tertile of skeletal muscle mass inversely associated with the incidence of NAFLD compared to the lowest tertile after adjusting for several known risk factors. Among subjects with NAFLD at baseline, the highest tertile of skeletal muscle mass was associated with resolution of NAFLD.

This study had several limitations. NAFLD was defined by hepatic steatosis index, not by imaging or biopsy. In addition, although there was an association between incident NAFL and sarcopenia, such an association was not observed between incident NASH or fibrosis and sarcopenia which would be important in predicting mortality. The application of tertiles for muscle mass may not be practical in clinical practice. A user-friendly discrete cut-off is perhaps more prudent, but would require separate validation. In their multivariate model, the hepatic steatosis index includes body mass index and diabetes in its calculation, and therefore adjusting for diabetes and waist circumference is problematic without univariate analyses. Finally, this study was performed in a Korean population, as with most prior work in this field, so it remains to be seen if this generalizes to other ethnicities. However, taken together with the larger body of evidence, this study

suggests that increases in relative skeletal muscle mass led to benefits in both a lower incidence of NAFLD and the resolution of existing NAFLD. Future studies are needed to investigate the impact of behavioral interventions that target both sarcopenia and improved muscle function, as a measure for (I) maintenance of individual functional status, and (II) impact on secondary disease processes such as NAFLD and NASH.

From a pathophysiological perspective there is significant overlap between the mechanisms underlying NAFLD and sarcopenia, with complex interplay between shared mechanisms including insulin resistance and growth hormone dysregulation through the insulin-like growth factor 1 axis, systemic inflammation, myostatin and adiponectin homeostasis, nutritional deficiencies such as vitamin D, hepatic production of catabolic factors, and physical deconditioning/immobility (8,9).

Lifestyle modification, including physical activity is the current mainstay for the management of NAFLD. Likewise, physical resistance activity is the primary strategy in preventing and managing sarcopenia. Physical activity has been shown to enhance functional capacity and increase muscle mass, including in patients with cirrhosis (10). Adequate protein intake while reducing fat and fructose intake is recommended to prevent sarcopenia (11). With recognition of a significant link between sarcopenia and NAFLD, incorporating both adequate dietary changes and resistance physical activity should be considered in designing therapeutic strategies for patients with sarcopenia in the setting of NAFLD. Providers should address sarcopenia as a potentially disease-modifying intervention in patients with NAFLD and/or NASH.

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Footnote

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

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