Editorial

Building mass to prevent non-alcoholic fatty liver disease?

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While increased adiposity, generally estimated by high body mass index (BMI) is the major risk factor for non-alcoholic fatty liver disease (NAFLD), several studies have now reported an association between low skeletal muscle mass and this condition (1,2). In particular, sarcopenia has been associated with NAFLD in the general population, and with disease severity in patients who underwent liver biopsy (3-5).

The pathophysiological mechanisms of sarcopenia, that is of inappropriately low muscle mass, are multifactorial and not fully understood. It remains unclear whether sarcopenia plays a causal role in NAFLD or whether it is a marker of more severe insulin resistance or systemic inflammation. However, sarcopenia and NAFLD share similar mediators. For example, insulin resistance is significantly associated with sarcopenia. Loss of muscle mass reduces a key cellular target for insulin, contributing to glucose intolerance and promoting gluconeogenesis, which exacerbates proteolysis and muscle depletion. Moreover, in adipose tissue insulin resistance results in enhanced lipolysis and availability of free fatty acids, which are taken up by the liver if not by the muscle, ultimately resulting in NAFLD. The association between sarcopenia and NAFLD may also be explained by activation of inflammatory pathways, such as those driven by interleukin-6 and nuclear factor kappa B, that are frequently turned on in NAFLD and that induce protein catabolism (3,6).

Other mechanisms explaining sarcopenia comprise myokine mediators, that are circulating factors with hormone activity released by myocytes. For example, myostatin is a potent negative regulator of skeletal muscle growth, but the myostatin receptor is expressed by hepatic stellate cells. This raises the question as to whether NAFLD-related sarcopenia is caused by myostatin activation in skeletal muscle, or sarcopenia is the primary abnormality related to myostatin, and consequently function in an endocrine manner thus activating fibrogenic hepatic stellate cells. Irisin, the cleaved extra-cellular fragment of the Fibronectin type III domain-containing protein 5 (FNDC5), another exercise-inducible myokine with favorable metabolic activity, is also involved in the control of energy expenditure, body weight, and regulation of insulin resistance (7,8). Recently an association among variants in the *FNDC5* gene, in particular rs3480 (G) allele, and severe steatosis and fibrosis has emerged (8,9). Elevated serum irisin was moreover associated with reduced steatosis, and an improved metabolic profile (8). Finally, Growth differentiation factor 15 (GDF15), an endocrine hormone belonging to the TGFβ superfamily, is over-expressed in muscle-wasting conditions. As sarcopenia was independently associated with NASH, circulating GDF15 levels might influence the histological severity of NAFLD by controlling muscle mass (10). Skeletal muscle can thus be considered an endocrine organ, which secretes peptides affecting liver function. It is therefore plausible that sarcopenia plays a causative role in fatty liver through altered secretion of various myokines.

In a recent study, Kim *et al.* (11) examined in a longitudinal population-based cohort of 2,943 subjects with

and 12,624 without baseline NAFLD with a 7-year follow-up whether relative skeletal muscle mass and changes in relative muscle mass were associated with the development or the resolution of this condition. The diagnosis of NAFLD was established according to the hepatic steatosis score (HSI), while skeletal muscle mass was evaluated using bioelectrical impedance analysis and expressed by skeletal muscle mass index (SMI), a measure of body weight-adjusted appendicular skeletal muscle mass. As compared with the lowest tertile, patients in the highest SMI tertile were protected against incident NAFLD [adjusted hazard ratio, AHR =0.44; 95% confidence interval (CI) =0.38–0.51] and more likely to experience resolution of baseline NAFLD (AHR =2.09, 95% CI =1.02–4.28), regardless of sex, age, waist circumference, diabetes, hypertension, smoking status and the level of physical exercise. A novel finding was that subjects in the highest tertile of SMI increase over a year demonstrated a beneficial association with incident NAFLD (AHR =0.69, 95% CI =0.59–0.82) and resolution of baseline NAFLD (AHR =4.17, 95% CI =1.90–6.17), which was also independent of baseline SMI. This observation is important, because it validates the association between muscle mass and protection from liver disease prospectively, and suggest that interventions aimed at increasing SMI may lead to NAFLD resolution.

These data complement those from previous studies reporting similar results (reported in *Table 1*). In particular, Hong *et al.* (1) reported in an observational cohort study involving 452 healthy subjects from South Korea an increased risk of NAFLD, as estimated by liver attenuation index at computed tomography (CT) in individuals with lower SMI calculated by dual energy X-ray absorptiometry (DXA). The association between SMI and NAFLD was confirmed by Lee *et al.* (3), in a cross sectional study in which 15,132 Asian subjects were enrolled. Besides, patients with lower SMI were more likely to have advanced fibrosis estimated by BARD or FIB-4 scores (3). Interestingly the risk of NAFLD was lower in individuals taking regular exercise. In another study (4) evaluating 309 Asiatic subjects with liver histology and bioelectrical impedance analysis (BIA), a higher prevalence of sarcopenia was detected in patients with NAFLD and NASH and there was an inverse correlation between appendicular skeletal muscle mass (ASM) and the severity of fibrosis. Sarcopenia resulted associated with NAFLD (although not independently of metabolic confounders) and with significant fibrosis independent of BMI and insulin resistance. Moreover, patients with reduced muscle mass were more prone to have NASH, regardless of age, gender, BMI, hypertension, diabetes, smoking status and insulin resistance. Petta *et al.* (5) examined skeletal muscle mass and liver histology in 225 consecutive Western patients with NAFLD. A higher prevalence of sarcopenia in patients with severe fibrosis and an association between sarcopenia and severe steatosis were found, which persisted after adjustment for confounders. A direct association between sarcopenia and NAFLD was confirmed by Choe *et al.* (2) in a retrospective study involving 1,828 subjects from South Korea evaluated for liver steatosis by ultrasonography and skeletal muscle mass by CT. Nevertheless, after correcting for sex, age, ethnicity, obesity or insulin resistance sarcopenia did not result associated with prevalent NAFLD in 9,985 individuals included in the NHANES-III study, where liver steatosis was investigated by US and skeletal muscle mass by MRI and bioelectrical impedance formula (OR =1.00, 95% CI =0.79–1.27) (12).

All in all, the majority of studies seem to suggest a close link between NAFLD and skeletal muscle mass. Limitations however are still to be considered. First of all, quite a large heterogeneity in the definition of NAFLD remains. For instance, the presence and the grade of hepatic steatosis have been evaluated by using different methods (US, CT, liver histology, noninvasive scores) and only two among the works presented refer to liver biopsy for the diagnosis of NAFLD. The same is valid for the evaluation of skeletal muscle mass that has been examined by BIA, DXA or CT. Moreover, the role of physical exercise, namely type, duration, frequency and the possible use of dietary supplementations have not systematically been evaluated. Importantly, a note of caution is necessary regarding patient selection. Because most of the studies enrolled mainly individuals of Asian ethnicity, the conclusions might not be generalizable to other ethnic populations.

Nevertheless, given the significant association between low skeletal muscle mass and NAFLD, and the novel data suggesting that its increase is linked to reduction in indices of hepatic fat accumulation, building muscle mass could be a novel strategy for the prevention and management of this disease. Additional longitudinal and interventional studies evaluating more accurately muscle metabolic and endocrine function together with liver damage are still necessary to confirm these findings, and to identify the best approaches to achieve higher SMI before this approach can be recommended in clinical practice.

Table 1 Characteristics of the studies exploring the relationship between skeletal muscle mass and NAFLD spectrum

Authors	Design; No. of subjects; ethnicity	Skeletal muscle mass measurement	Steatosis evaluation	Main results
Hong *et al*. (1)	Prospective observational cohort study; 452 healthy subjects; South Korea	SMI measured by DXA	Liver attenuation index (LAI), by abdominal CT	OR of NAFLD 5.16 (95% CI, 1.63–16.33) in the lowest *vs.* highest SMI quartile
Lee *et al.* (3)	Cross sectional study; 15,132 subjects; South Korea	SMI measured by DXA	Hepatic steatosis index (HSI), comprehensive NAFLD score and NAFLD liver fat score	SMI inversely correlated with NAFLD predicting scores. ↑NAFLD regardless of obesity (OR =1.55–3.02) or metabolic syndrome (OR =1.63–4.00) in sarcopenic subjects. Subjects with NAFLD and lower SMI more likely to have advanced fibrosis (BARD and FIB-4: OR =1.83 and 1.69, respectively; both P<0.001). Lower risk of NAFLD in individuals who exercised regularly
Shen *et al.* (12)	Cross sectional study; 9,985 subjects; United States (multi-ethnic)	Bioelectrical impedance formula validated using magnetic resonance imaging-measured skeletal mass	Abdominal US	Sarcopenia not associated with prevalent NAFLD (OR 1, 95% CI, 0.79–1.27) regardless of sex, age, ethnicities, obesity or insulin resistance
Koo *et al*. (4)	309 subjects; South Korea	ASM measured by BIA	Liver biopsy	↑ sarcopenia in subjects with NAFLD and NASH (P<0.001). ASM inversely correlated with the severity of fibrosis (P<0.001). ↑ significant fibrosis (≥F2) in subjects with sarcopenia (P<0.001). Sarcopenia associated with NAFLD (OR 3.82; 95% CI, 1.58–9.25), lost after adjustment for BMI, diabetes, hypertension. ↑ NASH in sarcopenic adjusted for age, gender, BMI, hypertension, diabetes, smoking (OR, 2.28; 95% CI, 1.21–4.30) and insulin resistance (OR, 2.30; 95% CI, 1.08–4.93). Sarcopenia associated with significant fibrosis independent of BMI and insulin resistance (OR, 2.05; 95% CI, 1.01–4.16)
Petta *et al.* (5)	225 consecutive patients with histological NAFLD (Kleiner score); Italy	SMI measured by BIA	Liver biopsy	↑ sarcopenia in patients with severe fibrosis F3-F4 (adjusted OR 2.36, 95% CI, 1.16–4.77). Significant association between sarcopenia and severe steatosis (OR 2.02, 95% CI, 1.06–3.83)
Choe *et al*. (2)	Retrospective study; 1,828 subjects; South Korea	Skeletal muscle mass measured by CT	Abdominal US	↑ NAFLD in sarcopenic subjects regardless of obesity. Sarcopenia associated with NAFLD (adjusted OR 1.51; 95% CI, 1.15–1.99)

↑, increase. ASM, appendicular skeletal muscle mass; BIA, bioelectrical impedance analysis; BMI, body mass index; CI, confidence interval; CT, computed tomography; DXA, dual energy X-ray absorptiometry; OR, odds ratio; SMI, skeletal muscle mass index (%) = total skeletal muscle mass (kg)/weight (kg) ×100; US, ultrasonography; NAFLD, non-alcoholic fatty liver disease.

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Footnote

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