



Sarcopenia in non-alcoholic fatty liver disease: Targeting the real culprit?

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There is exponential interest in non-alcoholic fatty liver disease (NAFLD) as a cause of chronic liver disease in the last decade [1]. The epidemic of obesity due to changes in life style and nutritional habits in Western countries has greatly contributed to the rapid increase in prevalence of NAFLD. In addition to obesity, NAFLD is strongly associated with diabetes mellitus and insulin resistance that are believed to be a consequence of low physical activity and increased fat mass as well as the metabolic syndrome [2,3].

The first observation that a reduction in muscle tissue (better known as sarcopenia) could be involved in NAFLD came from the Korean Sarcopenic Obesity Study [4]. The authors found that individuals with age-related sarcopenia which was associated with higher body mass index (BMI) and fat mass had an increased prevalence of NAFLD. By analyzing the same database, previous studies had shown that, during aging, the increase in fat mass and the decrease in muscle mass resulted in an increase in metabolic disorders [5]. Type 2 diabetes has also been found to be independently associated with sarcopenia [6]. These studies have led to the hypothesis that leptin and other adipocytokines from the adipose tissue increase muscle catabolism and consequent sarcopenia and reduced physical activity which, through a vicious cycle, results in increased fat accumulation and weight gain.

In this issue of *Journal of Hepatology*, Lee and coworkers [7] provide further information on the relationship between sarcopenia and NAFLD by analyzing the data from the Korea National Health and Nutrition Examination Survey.

The opportunity to derive data from this large population study was based on the application of non-invasive scores, with an acceptable positive predictive index, for the diagnosis of NAFLD. Dual-energy X-ray absorptiometry was used for the assessment of body composition to define changes in muscle mass. Sarcopenia was diagnosed using the skeletal muscle index (SMI) and defined as <1 standard deviation below the average of a young reference population.

The key finding of this study was the strong association between sarcopenia and NAFLD regardless of obesity or metabolic syndrome. Both non-obese and obese subjects showed a significantly increased prevalence of NAFLD when sarcopenia was present (non-obese non-sarcopenic: 4–14% vs. non-obese sarcopenic: 9–30%; $p < 0.001$, and obese non-sarcopenic 50–72% vs. obese sarcopenic 61–83%; $p < 0.001$). Similar results were found when patients were stratified by the presence or absence of metabolic syndrome. Interestingly, the authors also examined the impact of regular exercise in patients with NAFLD and found that in obese subjects with preserved skeletal muscle mass, regular exercise was associated with a reduced probability of NAFLD (46 vs. 55% $p < 0.001$). Furthermore, among patients with NAFLD, the presence of sarcopenia was also independently associated with a higher probability of advanced liver fibrosis (evaluated through fibrosis predictors).

It is important to note that in the study by Lee, diagnosis of sarcopenia was made using the SMI, a ratio of the appendicular skeletal muscle (ASM) and body weight (BW). SMI may decrease when the fat mass is enhanced, either for obesity or for aging, due to the increase in body mass and therefore the absolute decrease in muscle tissue may be lower than indicated [8]. Recently however, in a more limited group of patients, sarcopenia evaluated using computed tomographic (CT) scans, a method which allows precise quantification of muscle mass, was also reported to be associated to the development of NASH or NASH and cirrhosis [9,10].

An increasingly recognized limitation of body composition measurements is the difficulty of quantifying muscle mass with precision [11,12]. A number of methods have been described including DEXA and image analysis using CT or magnetic resonance imaging (MRI). A major limitation of CT and MRI despite their recognized accuracy in identifying skeletal muscle is due to their cost and logistics in population studies. DEXA remains the best option and even though DEXA measures non-fat mass and not muscle mass directly, appendicular non-fat, non-bone mass is predominantly skeletal muscle. Furthermore, the authors acknowledge that muscle mass can be measured using DEXA but the impact on quality of the muscle is not known. This is especially relevant since in type 2 diabetes mellitus, an insulin resistant state, inter- and intra-myocellular fat are increased.

* DOI of original article: <http://dx.doi.org/10.1016/j.jhep.2015.02.051>.

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Editorial

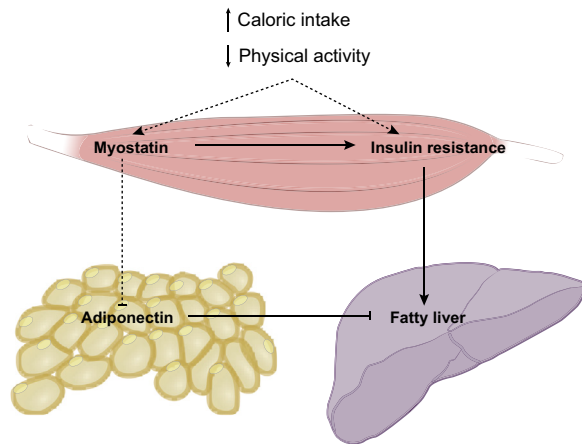


Fig. 1. Skeletal muscle centric approach to non-alcoholic fatty liver disease (NAFLD). Myokines, specifically myostatin, cross-talk with adipocytokine, adiponectin contributes to the development and progression of NAFLD.

Neither muscle function or strength were measured in the study by Lee [7] and it is not clear if the sarcopenia in patients with NAFLD and metabolic syndrome is associated with reduced muscle strength. Contractile function of the muscle does correlate with outcomes in chronic diseases but whether such an association exists in metabolic dysfunction is not known at this time.

To understand if the association between sarcopenia and NAFLD is a cause or a consequence, there is a need to identify the possible pathophysiological mechanism relating muscle, adipose tissue and the liver. Recognition that the skeletal muscle is an endocrine organ secreting various myokines may help to understand its role in the development of fatty liver [13] (Fig. 1).

Focusing on the skeletal muscle and on the mediators that link the muscle-liver-adipose tissue axis, is likely to provide a very novel and exciting area for therapeutic development [14,15]. A number of animal studies have shown that myostatin, a TGF β superfamily member, which was initially discovered as a regulator of skeletal muscle mass, has significant hepatic effects by regulating skeletal muscle metabolism. Blocking myostatin not only increases muscle mass but also protects mice from fatty liver and improves insulin resistance [16,17]. Furthermore, myostatin also promotes an increase in muscle mass depending on the time of exposure of adipocytes in their development [18]. Myostatin receptor, Activin IIb, has been reported, albeit in abstract form only, in hepatic stellate cells. This raises the interesting question of whether fatty liver results in sarcopenia via activation of myostatin in the skeletal muscle, or whether is sarcopenia the primary abnormality mediated by myostatin that functions in an endocrine manner to activate the fibrogenic hepatic stellate cells. Adiponectin is another potential mediator of the adipose tissue muscle axis that alters hepatic metabolism. Adiponectin receptors in the muscle have been reported to regulate insulin signaling and increase fatty acid oxidation but whether there is an adiponectin-myostatin cross-talk has been speculated upon but never proven [15]. Obesity and adipose tissue inflammation are accompanied by hypo-adiponectinemia and adiponectin improves insulin signaling. Since myostatin increases adipose tissue mass, and this in turn decreases adiponectin secretion, the liver-muscle-adipose tissue perturbation may actually begin in the skeletal muscle and act on both the liver and adipose tissue. Interleukin-6 is another myokine that potentially regulates

hepatic fatty acid oxidation via an AMPK dependent mechanism. Secretory and signaling perturbations of other myokines that regulate lipid and glucose metabolism that include myonectin and irisin have been suggested to contribute to the development of insulin resistance and fatty liver [19,20]. In addition to myokines regulating metabolism, skeletal muscle contributes to the resting energy and maximum energy expenditure [21]. Skeletal muscle mitochondrial dysfunction has been reported with muscle atrophy and whether impaired skeletal muscle substrate and energy utilization contribute to the development and progression of fatty liver is not known. Given the beneficial effects of increased physical activity on both the hepatic and non-hepatic components of the metabolic syndrome, targeting skeletal muscle mitochondrial function is another attractive approach to treat metabolic disorders including NAFLD.

The present study adds to the existing literature on sarcopenia and its impact on severity and possibly outcomes in NAFLD. These are exciting translational human data generated from basic biology of the muscle-liver axis that provide a compelling rationale to study the skeletal muscle as a primary therapeutic target in NAFLD and metabolic syndrome. Although the study of Lee and coworkers has limitations, including the absence of histological diagnosis of NAFLD and the use of muscular indices, identifying a strong and direct contribution of the skeletal muscle to hepatic disease is likely to result in a broader therapeutic approach to NAFLD.

Financial support

SD is supported by grants NIH DK83414 and NIH DKUDK 061732.

Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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