Editorial Commentary

Lean individuals with nonalcoholic fatty liver disease, the chicken or the egg?

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With the increasing obesity population, the prevalence of nonalcoholic fatty liver disease (NAFLD) has continuously grown in recent decades (1). It has recently been recognized that NAFLD can be presented in lean or non-obese individuals. This subset of individuals, referred as "lean NAFLD" or "non-obese NAFLD", accounts for approximately a quarter of entire NAFLD population (2). Although there are some debates, genetic disorders (lipodystrophies, *PNPLA3*, *TM6SF2*, *CETP* polymorphism), insulin resistance with increased visceral adiposity, infections (hepatitis C virus, human immunodeficiency virus), and dysbiosis of the gut microbiota are regarded as etiologies of lean NAFLD (2). The definition of lean NAFLD based on the body mass index (BMI) which is calculated by height and weight, thereby, the term "lean" could not reflect the entire adiposity or muscle mass. The BMI based obesity definition would misguide our understanding in NAFLD pathophysiology. Among lean NAFLD, individuals with low BMI and higher visceral adiposity can be existed, and they likely to have much more metabolic dysfunction due to the increased visceral adiposity. Those with lean NAFLD with high visceral adiposity tends to have unfavorable metabolic features, which leads to poor prognosis. This heterogeneity of lean NAFLD (with or without increased visceral adiposity) could contribute to the controversy of the long term-outcome of lean versus obese NAFLD.

In this issue of *Hepatology*, Nabi *et al.* (3) demonstrated that NAFLD in lean individuals tend to have more severe hepatic fibrosis and are associated with increased risks for liver related events, chronic kidney, and overall mortality in a nationwide French cohort during 3.58 years of follow-up period. Although lean NAFLD individuals were younger and had less proportion of diabetes, hypertriglyceridemia, and hypercholesterolemia at baseline compared to non-lean NAFLD group, the proportions of those with elevated liver enzymes (alanine transaminase, and gamma-glutamyl transpeptidase) and advanced liver fibrosis were higher in lean NAFLD individuals. Moreover, Asian ethnicities and the proportion of increased alcohol intake (>10 g/day but less than 30 g/day for men and 20 g/day for women) were more likely to be identified as lean NAFLD. Although the current study did not have any information on liver images, histology or insulin resistance, the authors described that insulin resistance which more increase in lean NAFLD than obese NAFLD could be a clue for explaining the results. Considering that insulin resistance is a fundamental component in NAFLD progression, the muscle mass/function and visceral adiposity which are largely affected by insulin resistance, can also contribute to the development of NAFLD (4). Recent evidences support the dense

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association between sarcopenia, NAFLD and advanced liver fibrosis (5,6). Furthermore, muscle quality could determine the severities of NAFLD (4,7). Besides the role of visceral adipose tissue in lipid oxidation and accumulation (8,9), skeletal muscle also plays a crucial role in fatty liver metabolism through secreting various myokines. Interleukin-6 involves hepatic glucose metabolism and lipogenesis in liver (10), while irisin involves lipogenesis through sterol regulatory element-binding protein 2 and fatty acid beta-oxidation in liver (11). Therefore, muscle impairment by metabolic dysregulation would be an early phenotype of NAFLD. A 7-year longitudinal study also demonstrated that decreased skeletal muscle mass increases the incidence of NAFLD (12). Lean NAFLD individuals likely to have sarcopenia, and the prevalence of sarcopenia in NAFLD population is significantly higher than that of healthy individuals (13). NAFLD *per se* rarely increases overall mortality (14), while when it combined with sarcopenia more complicated features are observed (5,14), thus sarcopenia would be the key factor for determining the prognosis in individuals with NAFLD. Regarding the elevated liver enzymes and a higher prevalence of advanced liver fibrosis in lean NAFLD as Nabi *et al.* (3) reported, the term, "lean NAFLD" might be a complicated feature of NAFLD and a late consequence of NAFLD pathophysiology, rather than another phenotype of NAFLD.

If lean NAFLD is more harmful and advanced, than obese/overweight NAFLD, then can body weight gain reverse the clinical outcomes in lean NAFLD? The answer would be a half yes and a half no. Regarding that NAFLD is a phenotype of ectopic fat accumulation, visceral adiposity is another key factor for determining clinical feature for lean NAFLD. In a 22.4-year longitudinal study, the mortality risk of lean NAFLD patients with increased waist circumference was higher than that of obese/overweight NAFLD patients (15). Interestingly, the BMI value was not associated with mortality risk while waist circumference was associated with increased both overall and cardiovascular disease mortality. This study highlights the role of visceral adiposity in lean NAFLD. Like shown in results of Nabi *et al.* (3) more Asian population tend to have lean NAFLD, due to the increased visceral adiposity with a relatively lower BMI in Asians compared to other ethnic groups. Although BMI and waist circumference are correlated, the clinical implication of those two parameters would be different. In terms of obesity, the measurement of BMI can present overall adiposity including muscle and bone mass, while waist circumference can estimate visceral adiposity. The association between sarcopenia and NAFLD appears in both the non-lean and lean NAFLD individuals (6). When NAFLD is combined with sarcopenia, the risk of cardiovascular disease increases independent of BMI-based obesity (5). The aforementioned evidences suggest the need for a new anthropometric index to predict clinical outcomes other than BMI. To manage NAFLD, decreasing visceral adiposity and increasing muscle mass/quality would be more important than simply decreasing body weight as body weight is a crude parameter.

In the context of NAFLD management, Nabi *et al.* (3) provided clinical implications for a close monitoring in lean populations, for liver related events and chronic kidney disease as well as death. Although the authors did not measure the waist circumference or muscle mass/quality in the current study, the adverse outcomes in lean NAFLD might be associated with sarcopenia and visceral adiposity (14). Therefore, the improvement in those two risk factors would be the main strategies for NAFLD treatment regardless of BMI changes. A longitudinal study clearly demonstrated that resolution of NAFLD was observed in NAFLD individuals who experienced increase in skeletal muscle (12). To achieve increasing muscle mass/quality and reducing visceral adiposity, physical activity is recommended. Physical activity can enhance insulin sensitivity in adipose tissue, liver, and skeletal muscle, which are the triad in NAFLD development. Furthermore, exercise can promote the secretion of beneficial myokines, which lead to improvement in systemic insulin resistance, and hepatic inflammation (10,11). The sedentary lifestyle is one of the major risk factors for NAFLD (15), whereas, exercise lowers the risks of NAFLD (6). Although there are limited data on the impact of physical activity types, intensity, duration, and frequency in NAFLD, most guidelines recommend moderate to vigorous physical activity to individuals with NAFLD. A recent study reported that increased leisure time activity (≥300 min/week) decreased NAFLD risk by 37% with statistical significance (13).

In summary, the study by Nabi *et al.* (3) highlights that lean NAFLD is a complicated phenotype of NAFLD with poorer clinical outcomes, thus, needs close surveillance for those populations. Although the term "lean NAFLD" is generally established, the pathophysiology or clinical prognosis of individuals with lean NAFLD should be

further investigated. As recent evidences demonstrated the strong association between NAFLD and skeletal muscle, especially focusing on sarcopenia and myosteatosis (6,12-14), the causality of those diseases should be clarified in longitudinal prospective trials which will further enhance our understanding of NAFLD complexity, and help to build a NAFLD management strategy. Moreover, a brand-new obesity index other than BMI-based obesity index may be needed, and cardiometabolic risk factors should be assessed among non-obese individuals with hepatic steatosis to identify lean NAFLD at a higher risk.

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