Lean or Non-obese Nonalcoholic Fatty Liver Disease Patients: Are They Really Lean?

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The prevalence of nonalcoholic fatty liver disease (NAFLD) has dramatically increased in recent decades, parallel with the expansion of the obese population. However, a substantial number of individuals with NAFLD are lean. The proportion of lean or non-obese and obese NAFLD patients among those with NAFLD is 19.2% and 40.8%, respectively. The definition of lean or non-obese is based on body mass index (BMI) with ethnic-specific cut-off points. Given the lower prevalence of NAFLD in the Asian countries compared to that in Western countries and the comparable proportion of lean or non-obese proportion of NAFLD between those populations, the Asian population, with a relatively lower BMI is more vulnerable to NAFLD. Moreover, Asians tend to have more visceral fat deposition with a similar BMI compared to other ethnicities. Therefore, lean or non-obese NAFLD was considered a unique phenomenon among Asians in early studies, which is why most studies were conducted in Asian countries.

In this issue of Clinical and Molecular Hepatology, Kim et al. demonstrated that visceral fat obesity had the strongest association with non-obese NAFLD, the impact of which is greater than that of diabetes or systemic inflammation. Although the pathophysiological mechanisms of non-obese or lean NAFLD are unclear, growing evidence supports that visceral obesity rather than BMI-based obesity plays a crucial role. The association between sarcopenia, myosteatosis, and NAFLD is based on insulin resistance, and myosteatosis rather than sarcopenia determines the early stage of NAFLD progression. Given that lipid oxidation capacity regulated by visceral adiposity controls lipid accumulation in muscle, visceral adiposity might be the main and early phenotype of lean or non-obese NAFLD individuals as well as obese NAFLD individuals. Therefore, the BMI-based obesity index does not accurately reflect visceral adiposity or obesity. Kim et al. reported no statistical difference in the visceral to subcutaneous fat ratio between non-obese and obese NAFLD patients in the male population, although the values of those with NAFLD were higher than those without NAFLD. Another Korean population-based study reported that visceral adiposity was the main contributor to incident NAFLD, with a baseline mean BMI of 23.7 kg/m² indicating that most individuals were non-obese; however, the mean waist circumference was 85.1 cm. Considering the sex ratio (40.2% female) and waist circumference cut-off value for central obesity in Asian women (85 cm), a substantial number of individuals were centrally obese with a normal BMI.

NAFLD and nonalcoholic steatohepatitis are well-established risk factors for cardio-renal and metabolic diseases as well as advanced liver diseases such as cirrhosis and cancers. Although
some data suggest that lean NAFLD individuals have less-severe disease and may have a more favorable outcome than their obese counterparts.\textsuperscript{14} Lean NAFLD individuals also experienced both hepatic and extrahepatic complications.\textsuperscript{15-17} The histological severity in non-obese NAFLD compared to obese counterparts seemed similar in terms of lobular inflammation and ballooning.\textsuperscript{14,15,18} In longitudinal biopsy-proven NAFLD studies, the mortality risk of lean or non-obese NAFLD patients is similar to that of obese NAFLD patients.\textsuperscript{15,18} A Chinese study demonstrated a better outcome in non-obese NAFLD patients compared to obese NAFLD patients, where the authors enrolled more individuals with liver fibrosis (55.1\% vs. 80.1\% for non-obese NAFLD vs. obese NAFLD, respectively) or those with metabolic syndrome (43.1\% vs. 69.8\% for non-obese NAFLD vs. obese NAFLD, respectively) in the obese group.\textsuperscript{14} The follow-up duration was relatively short (median 49 months) for determining mortality. Nevertheless, the results indicated that risk factors such as hypertriglyceridemia and increased creatinine levels were associated with NAFLD progression in lean patients, suggesting that dysregulated metabolic profiles are key to disease prognosis. In this context, metabolic dysregulation, instead of BMI-based obesity, may better reflect the clinical outcomes of NAFLD. Lean NAFLD individuals with metabolically unhealthy profiles have a higher risk for cardiovascular disease than obese NAFLD individuals.\textsuperscript{19} Likewise, the association between NAFLD and sarcopenia was strengthened in metabolic dysfunction.\textsuperscript{20} In terms of sarcopenia as one of the predisposing phenotypes of NAFLD, the association between sarcopenia and NAFLD appears in both the obese and non-obese NAFLD populations,\textsuperscript{20} even though Kim et al.\textsuperscript{4} did not report a statistically significant association between sarcopenic obesity and NAFLD, probably due to the small sample size of sarcopenic individuals with higher BMI. When NAFLD is combined with sarcopenia, the risk of cardiovascular disease increases regardless of obesity.\textsuperscript{21} The above evidence suggests the need for a new index to predict cardiometabolic risk other than BMI.

In terms of NAFLD management, especially in lean populations, Kim et al.\textsuperscript{4} provided clinical implications for body composition as a treatment goal. Reducing visceral fat and improving muscle quality and mass, instead of reducing body weight, were the main strategies for NAFLD treatment. In a Korean study with a median 4.4-year follow-up, NAFLD was resolved in 24.7\% of individuals, whose visceral adipose tissue amounts were significantly reduced, indicating a close relationship between visceral adiposity and NAFLD risk.\textsuperscript{11} Physical activity is recommended because it improves insulin resistance in adipose tissue, liver, and skeletal
muscle, the triad in NAFLD development, and improved muscle function further ameliorates systemic insulin resistance, and hepatic inflammation can be resolved.\textsuperscript{22} Exercise can ameliorate the risks of NAFLD,\textsuperscript{20} and liver fibrosis, even in individuals with sarcopenia.\textsuperscript{23} Additionally, physical exercise improves cardiopulmonary fitness, which can decrease cardiovascular events and mortality. Although there are limited data on type or duration of exercise on NAFLD regression, moderate to vigorous exercise might be helpful. A cross-sectional study showed that physical activity over 880 metabolic equivalent task-min/week decreased the risk of fibrosis, sarcopenia and cardiovascular disease.\textsuperscript{24}

In summary, the study by Kim et al. supported the evidence that visceral obesity is a risk factor for sarcopenia and/or myosteatosis in non-obese NAFLD individuals. This result was consistent with that of NAFLD as an ectopic fat deposit that manifested as visceral obesity, sarcopenia, and myosteatosis. Although the term “lean or non-obese” NAFLD individuals is widely accepted, the natural history or clinical prognosis of lean or non-obese NAFLD patients is comparable to that of obese NAFLD patients. Therefore, the BMI-based obesity index may need to be revised, and metabolic dysfunction should be considered to identify high-risk individuals with NAFLD. Moreover, NAFLD treatment strategies, besides reducing body weight should be established to improve body composition, which includes reduction of visceral adipose tissues, and increment of muscle mass/quality.
References