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Editorial

Lean vs. obese phenotypes of nonalcoholic fatty liver disease: similar or different?

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Nonalcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease worldwide, and its incidence and related complications are expected to rise with the global increase in metabolic disorders.[1] Traditionally, NAFLD has been closely associated with obesity and metabolic dysfunction, including insulin resistance, abnormal lipid profiles, and fatty acid cytotoxicity.[2] Despite the close association between NAFLD and obesity, NAFLD is increasingly being identified in non-obese populations.[3] A recent systematic review and meta-analysis reported that around 40% of the global NAFLD population was classified as non-obese (body mass index [BMI] <30 kg/m^2 in non-Asians; 25 kg/m^2 in Asians) and almost a fifth as lean (BMI <25 kg/m^2 in non-Asians; <23 kg/m^2 in Asians).[3] Clinical outcomes, such as the severity of metabolic dysfunction or the incidence of severe liver disease or mortality, of non-obese or lean individuals with NAFLD compared with obese individuals with NAFLD remain unclear due to variation across recent studies.

A recent meta-analysis of NAFLD reported that the degree of metabolic dysfunction was weight-dependent, with significantly less metabolic dysfunction in lean subjects compared with their overweight counterparts.[4] Another systematic review showed that the incidence (per 1,000 person-years) of all-cause (12.1 vs. 7.5), liver-related (4.1 vs. 2.4), and cardiovascular mortality (4.0 vs. 2.4) was relatively higher, and that of new-onset cardiovascular disease (CVD) was lower (18.7 vs. 33.3) in non-obese or lean patients with NAFLD than in obese patients with NAFLD.[3] In contrast, a recent longitudinal cohort study of 646 patients with biopsy-proven NAFLD reported that compared to non-lean patients with NAFLD (n=523, 81%), lean patients with NAFLD (n=123, 19%) with a low severity of liver fibrosis had no increased risk for overall mortality, but did face increased risk of developing severe liver disease (hazard ratio=2.69) during a mean follow-up of 19.9 years.[5]

In the current issue of *Clinical and Molecular Hepatology*, Chan made some points about the possible reasons for these disparities.[6] As mentioned in the review,[6] studies may be confounded by selection bias. Lean patients with NAFLD ob-

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served in secondary or tertiary clinical settings and diagnosed via liver biopsy may have more severe liver disease than expected. In addition, Chan noted the lack of consideration for important confounding factors, such as changes in alcohol consumption and body weight over time. Although accurate assessment of alcohol consumption is a prerequisite to accurate diagnosis and treatment of patients with NAFLD, unreported alcohol consumption can play a role for NAFLD progression and can vary during follow-up. Indeed, in a recent prospective observational study of 114 patients with NAFLD, repeated moderate to excessive alcohol consumption was detected in 28.6% of patients with presumed NAFLD who were at risk of alcohol-related liver damage.[7] Interestingly, patients with repeated moderate or excessive alcohol consumption had a significantly lower BMI and fewer metabolic comorbidities.[7] This suggests the importance of accurate assessment of alcohol intake when evaluating the prognosis of non-obese or lean patients with NAFLD.

Changes in body weight during follow-up could affect sarcopenia along with aging in patients with NAFLD.[8] A recent large cohort study of 52,815 adult participants reported that 5-year changes in appendicular skeletal muscle mass were significantly higher in participants with NAFLD than in those without NAFLD (-281.3 g vs. -225.2 g).[9] Furthermore, muscle loss was much faster in participants with NAFLD and significant liver fibrosis than in those without.[9] Therefore, it may be the influence of sarcopenia that non-obese or lean patients with NAFLD have a poor prognosis, although they have fewer metabolic dysfunctions. As such, an appropriate assessment of sarcopenia is important in clinical studies. In addition, the etiology of NAFLD in lean individuals may be based on central obesity and visceral fat.[10] Accordingly, the body weight-based BMI-driven approach for the classification of NAFLD may need to be reappraised.

In recent years, a number of genomic studies showed that genetic polymorphisms in the several genes, such as patatin-like phospholipase domain-containing-3 (PNPLA3) and transmembrane 6 superfamily member 2 (TM6SF2), can be a major genetic determinant of NAFLD and its severity.[11] A recent population-based study of 904 Asian subjects diagnosed with hepatic steatosis with proton-magnetic resonance spectroscopy reported that lean individuals were more likely to have a PNPLA3 gene polymorphism than overweight and obese ones, and the associations between PNPLA3 gene polymorphisms and NAFLD and between TM6SF2 gene polymorphisms and triglycerides level were stronger in lean than overweight and obese subjects.[12] Therefore, genetic polymorphisms may have a greater effect on the risk of NAFLD and disease progression in non-obese/lean subjects, but inconsistent findings has been observed across different ethnic groups; in addition, the interaction between adiposity and genetic variants other than PNPLA3 gene polymorphisms on the development and progression of NAFLD have not been adequately evaluated in previous Asian studies. Further research is needed to address genetic variants in non-obese or lean patients with NAFLD.

Effective therapeutic strategies for NAFLD remain unclear, and lifestyle modification including physical activity is the cornerstone for the management of NAFLD.[13,14] In a recent randomized controlled trial of 154 community patients with NAFLD, a 12-month lifestyle intervention program involving regular exercise was an independent factor associated with remission of NAFLD in non-obese patients.[13] Indeed, half of non-obese patients achieved NAFLD remission with a 3–5% weight reduction; the same could only be achieved in obese patients with a 7–10% weight reduction.[13] Another recent cohort study of 11,690 patients with NAFLD reported that the prevalence of significant liver fibrosis (fibrosis-4 index: 3.0%→1.0%; NAFLD fibrosis score: 2.4%→0.4%) and a high probability of atherosclerotic CVD (10.3%→6.3%) significantly decreased with increasing amounts of physical activity by quartile in lean patients with NAFLD.[14] These results showed that lifestyle intervention could be effective in treating NAFLD in non-obese patients.

Currently, there are no effective approved pharmacologic treatments for NAFLD.[15] Moreover, since most clinical trials related to drug development target patients with NAFLD and severe obesity, it is unclear whether these drugs can be applied equally to non-obese or lean patients with NAFLD. Vitamin E and pioglitazone were efficacious for biopsy-proven nonalcoholic steatohepatitis (NASH) in clinical practice; however, these agents should be used with caution in selected

Abbreviations:

BMI, body mass index; CVD, cardiovascular disease; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; PNPLA3, patatin-like phospholipase domain-containing-3; TM6SF2, transmembrane 6 superfamily member 2

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patients due to the reported risk in both European and American guidelines.[15] A recent placebo-controlled, randomized study of 50 lean patients with NAFLD who underwent lifestyle modification interventions reported that a symbiotic supplement consisting of seven bacterial strains resulted in a significantly greater reduction in liver stiffness (transient elastography: 9.36 kPa→6.38 kPa in the symbiotic group and 7.92 kPa→7.16 kPa in the placebo group), insulin resistance, and inflammatory markers including high-sensitivity C-reactive protein and nuclear factor-κB activity than placebo after a 28-week treatment period.[16] Recently, randomized clinical trials have examined the efficacy of glucose-lowering agents for treating patients with biopsy-proven NASH, but most targeted obese patients with NAFLD.[17] Among these studies, a phase-2b randomized placebo-controlled trial of 276 non-obese (overweight) or obese patients with biopsy-proven NASH reported that elafibranor (120 mg dose), a dual peroxisome proliferator-activated receptor-α/δ agonist, was significantly associated with a 2-point improvement in NAFLD activity score (48% elafibranor vs. 21% placebo) without worsening fibrosis (20% elafibranor vs. 11% placebo).[18] However, large-scale clinical trials are needed to study the efficacy of glucose-lowering agents in non-obese or lean patients with NAFLD.

Non-obese or lean patients with NAFLD show clinical findings, such as insulin resistance or metabolic dysfunction, similar to those of obese patients with NAFLD; however, genetic polymorphisms and other factors may be responsible for NAFLD development in non-obese or lean individuals. Because time-dependent covariates such as changes in alcohol consumption or body weight are frequently encountered in patients with NAFLD, it is difficult to accurately evaluate the influence of time-dependent covariates on the prognosis of non-obese or lean patients with NAFLD. However, the general management and follow-up needs of non-obese or lean patients with NAFLD are similar to obese patients with NAFLD, and well-designed clinical studies for pharmacologic treatments on this population should be conducted in the future.

Authors' contribution

All authors were responsible for the interpretation of data, the drafting, and critical revision of the manuscript for important intellectual content.

Conflicts of Interest

The authors have no conflicts to disclose.

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