

VOLUME 29 NUMBER 2 April 2023

pISSN 2287-2728
eISSN 2387-285X

CLINICAL and MOLECULAR HEPATOLOGY

The forum for latest knowledge of hepatobiliary diseases



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Editorial

Non-obese or lean nonalcoholic fatty liver disease matters, but is it preventable or inevitable in light of its risk factors?

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Keywords: Non-alcoholic fatty liver disease; Risk factors; Obesity; Metabolic diseases; Epigenomics

See Article on <https://doi.org/10.3350/cmh.2022.0398>

To date, a majority of studies have focused on obese nonalcoholic fatty liver disease (NAFLD), which is mainly responsible for the Western NAFLD population. Nevertheless, a substantial number of individuals with NAFLD in the Asia–Pacific region is not obese. Approximately 40% of the global NAFLD population is not obese and one-fifth is lean.¹ Furthermore, non-obese or lean NAFLD and obese NAFLD populations show comparable histological severity and long-term hepatic or extrahepatic outcomes.² In this regard, recent studies have been conducted to identify relevant risk factors beyond obesity for lean or non-obese NAFLD.

In this issue of *Clinical and Molecular Hepatology*, Ko et al.³ address the various risk factors that contribute to the development and progression of NAFLD, focusing on the lean or non-obese phenotype. Recent evidence indicates that central obesity rather than obesity *per se* driven by body mass index

is associated with fibrosis severity in non-obese NAFLD.² Specifically, visceral adiposity plays a more important role in the pathogenesis of NAFLD than does subcutaneous adiposity in terms of changes in NAFLD status.⁴ Sarcopenia is bidirectionally associated with NAFLD, although myosteatosis rather than sarcopenia plays a more important role in the progression of early-stage NAFLD.⁵ In addition, other medical conditions, such as type 2 diabetes and genetic polymorphisms, may also affect the development and progression of NAFLD in a lean population. A high caloric or fructose diet is considered a modifiable risk factor for NAFLD regardless of obesity status. Given that NAFLD affects more than one-quarter of the global population and has become a threat to global health, researchers are encouraged to explore modifiable risk factors to establish an appropriate treatment for NAFLD.

Non-obese or lean NAFLD is associated with a subset of risk factors that cannot be modified: age, sex, ethnicity, and genetics. The prevalence of NAFLD increases with age. Indeed, the prevalence of NAFLD was approximately 42.2% higher

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Editor: Seung Up Kim, Yonsei University College of Medicine, Korea

Received : Mar. 2, 2023 / Accepted : Mar. 4, 2023

among people older than 50 years compared with those younger.⁶ Nonalcoholic fatty liver disease is usually more prevalent in men than in women. According to a meta-analysis of studies published between 2016 and 2021, 44.5% of men and 31.8% of women had NAFLD.⁶ However, postmenopausal women had more severe NAFLD than men of similar age.⁷ The prevalence of NAFLD varies across ethnicities. In the United States, Hispanics have the highest prevalence of NAFLD, whereas African Americans have the lowest despite their higher rate of obesity.⁸ Genetic factors also contribute to the development and progression of NAFLD. For example, genetic variants such as *PNPLA3* and *TM6SF2* have been shown to be associated with the histological severity of NAFLD.⁹ A dose-dependent association has been observed between the G allele in *PNPLA3* rs738409 and fibrosis progression.¹⁰ Moreover, a higher level of *AGXT2* expression regulated by rs2291702 has a protective effect against liver fibrosis in patients with NAFLD.¹¹

Non-obese or lean NAFLD is also associated with several risk factors that can be modified: metabolic health, circulating metabolites, muscle mass and quality, the gut microbiome, and diet. Although obesity contributes to the prevalence and severity of overall NAFLD, metabolic health status has a greater effect on histological severity in non-obese compared to obese NAFLD.¹² Altered circulating saturated sphingomyelin level is associated with the histological severity of non-obese NAFLD.¹³ Dysregulation of circulating unconjugated primary bile acids is also associated with nonalcoholic steatohepatitis (NASH) independent of obesity and diabetes.¹⁴ Crosstalk between the liver and muscle has a significant effect on the pathogenesis of NAFLD. Lower muscle strength and lower muscle mass are significantly associated with advanced fibrosis in the NAFLD population.^{15,16} Moreover, mortality risk was two-fold higher in individuals with both NAFLD and sarcopenia than in those with neither.¹⁷ Muscle quality (i.e., severe myosteatosis) rather than muscle quantity (i.e., lower muscle mass) is also significantly associated with NASH and fibrosis progression in early-stage NAFLD.⁵ Nonalcoholic fatty liver disease is substantially influenced by gut dysbiosis. Only individuals with non-obese NAFLD exhibit significant alterations in the diversity and

composition of the gut microbiome and in stool metabolites along with increasing fibrosis severity.¹⁸ This suggests that gut-directed pharmabiotics may be a promising preventive and therapeutic strategy against non-obese NAFLD.

Growing evidence suggests that several epigenetic factors are also linked to NAFLD. An accompanying alteration in gene expression is associated with liver injury and NASH. Based on an assay for transposase-accessible chromatin with sequencing, substantial differences were noted in chromatin accessibility in the genomes of patients with non-NAFLD, nonalcoholic fatty liver, or fibrotic NASH.¹⁹ In addition, the length of telomeres in liver tissue cells shortens as fibrosis stage advances in patients with biopsy-proven NAFLD, even after adjustment for age.²⁰

Non-obese or lean NAFLD is a multi-factorial and complex condition that is influenced by both modifiable and non-modifiable risk factors. Although several risk factors, such as age and genetics, cannot be changed, many other risk factors exist that can be altered through lifestyle modifications and therapeutic interventions. In the near future, gene-based precision medicine, including anti-sense oligonucleotides and RNA interference, may alter the effect of genes on the development and progression of NAFLD, rendering genetics modifiable. Further studies on genetics and epigenetics will contribute to understanding the pathogenesis of non-obese or lean NAFLD, allowing us to develop potential therapeutic options for this disease. Better knowledge of modifiable risk factors would also assist in preventing or retarding the progression of NAFLD.

Authors' contribution

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

Acknowledgments

This research was supported by a National Research Foundation of Korea (NRF) grant funded by the Korean government (MEST) (2021R1A2C2005820 and 2021M3A9E4021818), Research of Korea Centers for Disease Control and Prevention (2022-ER0902-01).

Abbreviations:

NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis

Conflicts of Interest

The authors have no conflicts to disclose.

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