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EDITORIAL

Is metabolic syndrome responsible for the progression from NAFLD to NASH in non-obese patients?

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Abbreviations

NAFLD	Non-alcoholic fatty liver disease
MS	Metabolic syndrome
NASH	Non-alcoholic steatohepatitis
VAT/SAT	Visceral adipose tissue area/subcutaneous adipose tissue area
PNPLA3	Patatin-like phospholipase domain-containing 3

Non-alcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease and is a risk factor for significant hepatic fibrosis [1, 2]. Since there are multiple pathogeneses for NAFLD, various subgroups are seen in patients with NAFLD [3]. "Non-obese NAFLD with metabolic syndrome (MS)" is one subgroup, and a noteworthy fact is that this subgroup is growing increasingly prevalent [4, 5]. However, limited information is available regarding the prevalence and risk factors for non-alcoholic steatohepatitis (NASH) and significant fibrosis in non-obese patients with NAFLD.

In this issue of the *Journal of Gastroenterology*, Kim et al. investigated the prevalence of NASH and significant fibrosis in non-obese patients with NAFLD and MS [6]. They found that NASH and significant fibrosis were seen in approximately 60% and 55% of non-obese patients with NAFLD and MS, respectively, and its prevalence did not significantly differ from those in obese patients with NAFLD and without MS. Thus, metabolic disorders promote progression to NASH and significant fibrosis in non-obese patients with NAFLD. Furthermore, they showed that the ratio of visceral adipose tissue area-to-subcutaneous adipose tissue area (VAT/SAT) was an independent factor for NASH or significant fibrosis in a dose-dependent fashion [6]. Thus, this study revealed an important pathogenesis of non-obese NAFLD with MS. Even in non-obese patients with NAFLD, a metabolically unhealthy phenotype can promote progression to NASH and significant fibrosis through an increase in the VAT/SAT ratio.

Non-obese patients with NAFLD have been reported to have a lower risk of steatohepatitis and advanced fibrosis [7], and a patatin-like phospholipase domain-containing 3 (PNPLA3) variant (rs738409 C>G) was the only factor associated with NASH or significant fibrosis in non-obese patients with NAFLD [8]. Thus, genetic alteration has been thought to be the main pathogenesis of progression to NASH and significant fibrosis in non-obese patients with NAFLD [9]. However, in this issue of the *Journal of Gastroenterology*, Kim et al. revealed that the VAT/SAT ratio was an independent factor for NASH or significant fibrosis in a dose-dependent fashion [6]. Tobari et al. reported that the prevalence of PNPLA3 risk alleles did not differ between non-obese and obese patients with NAFLD [10]. Li et al. reported that non-obese patients with NAFLD had comparable lifestyle habits, including overeating, sleep disturbances, and overtime work, as obese patients with NAFLD [11]. Moreover, Wong et al. recently reported that a reduction in body weight and waist circumference by lifestyle intervention was an independent factor associated

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with the remission of NAFLD in non-obese patients [12]. Taken together, along with genetic alterations, metabolic syndrome with visceral obesity seems to be an important pathogenesis even in non-obese NAFLD.

Non-obese NAFLD and obese NAFLD are classified based on BMI, which is mainly affected by adipose tissue and skeletal muscle mass. Therefore, patients with NAFLD and adiposis and muscle atrophy can be classified as non-obese NAFLD. In fact, physical inactivity is an independent predictor of NAFLD in non-obese subjects [13]. Skeletal muscle mass is also significantly lower in non-obese patients with NAFLD than in obese patients with NAFLD [10]. In addition, sarcopenia exacerbates obesity-associated insulin resistance [14], which is a potent risk factor for NASH and advanced hepatic fibrosis in patients with NAFLD. Recently, Vila et al. reported that the muscle-specific ubiquitin-conjugating E2O causes diet-induced insulin resistance and metabolic syndrome in mice [15]. Thus, loss of skeletal muscle mass could be a pathogenesis for NASH and advanced fibrosis in non-obese patients with NAFLD and metabolic syndrome.

In this issue of the *Journal of Gastroenterology*, Kim et al. clearly demonstrated that, regardless of BMI, metabolic syndrome was associated with the progression to NASH and significant fibrosis in patients with NAFLD [6]. However, there are limitations in this study. First, this study was designed as a cross-sectional study, and the causal relationship between metabolic syndrome and the progression to NASH and significant fibrosis remains unclear. Second, metabolic syndrome was defined by elevation of blood pressure, fasting blood glucose level, and serum triglyceride level, and reduction of high-density lipoprotein cholesterol level. It remains unclear which metabolic disorder has the most significant impact on the progression to NASH and significant fibrosis. Third, lifestyle-related factors including energy intake, mild alcoholic consumption, and physical activity, as well as the skeletal muscle mass of the trunk, were not analyzed in this study. These limitations should be examined in a future study to reveal further the pathogenesis of and establish therapeutic strategies for non-obese NAFLD.

Compliance with ethical standards

Conflict of interest Takumi Kawaguchi received lecture fees from Mitsubishi Tanabe Pharma Corporation, MSD K. K., and Otsuka Pharmaceutical Co., Ltd. The other authors have no conflicts of interest.

References

1. Kanwal F, Kramer JR, Mapakshi S, Natarajan Y, Chayanupatkul M, Richardson PA, et al. Risk of hepatocellular cancer in patients with non-alcoholic fatty liver disease. Gastroenterology. 2018;155:1828–37 **(e2)**.
2. Brar G, Tsukamoto H. Alcoholic and non-alcoholic steatohepatitis: global perspective and emerging science. J Gastroenterol. 2019;54:218–25.
3. Eslam M, Sanyal AJ, George J. Toward more accurate nomenclature for fatty liver diseases. Gastroenterology. 2019;157:590–3.
4. Nishioji K, Sumida Y, Kamaguchi M, Mochizuki N, Kobayashi M, Nishimura T, et al. Prevalence of and risk factors for non-alcoholic fatty liver disease in a non-obese Japanese population, 2011–2012. J Gastroenterol. 2015;50:95–108.
5. Stefan N, Schick F, Haring HU. Causes, characteristics, and consequences of metabolically unhealthy normal weight in humans. Cell Metab. 2017;26:292–300.
6. Kim D, Kim W, Joo SK, Han J, Kim JH, Harrison SA, et al. Association between body size-metabolic phenotype and nonalcoholic steatohepatitis and significant fibrosis. J Gastroenterol. 2019. https://doi.org/10.1007/s00535-019-01628-z.
7. Wei JL, Leung JC, Loong TC, Wong GL, Yeung DK, Chan RS, et al. Prevalence and severity of nonalcoholic fatty liver disease in non-obese patients: a population study using proton-magnetic resonance spectroscopy. Am J Gastroenterol. 2015;110:1306–14 **(quiz 15)**.
8. Fracanzani AL, Petta S, Lombardi R, Pisano G, Russello M, Consonni D, et al. Liver and cardiovascular damage in patients with lean nonalcoholic fatty liver disease, and association with visceral obesity. Clin Gastroenterol Hepatol. 2017;15:1604–11 **(e1)**.
9. Argo CK, Henry ZH. Editorial: "Lean" NAFLD: metabolic obesity with normal BMI.. is it in the genes? Am J Gastroenterol. 2017;112:111–3.
10. Tobari M, Hashimoto E, Taniai M, Ikarashi Y, Kodama K, Kogiso T, et al. Characteristics of non-alcoholic steatohepatitis among lean patients in Japan: not uncommon and not always benign. J Gastroenterol Hepatol. 2019;34:1404–10.
11. Li C, Guo P, Okekunle AP, Ji X, Huang M, Qi J, et al. Lean non-alcoholic fatty liver disease patients had comparable total caloric, carbohydrate, protein, fat, iron, sleep duration and overtime work as obese non-alcoholic fatty liver disease patients. J Gastroenterol Hepatol. 2019;34:256–62.
12. Wong VW, Wong GL, Chan RS, Shu SS, Cheung BH, Li LS, et al. Beneficial effects of lifestyle intervention in non-obese patients with non-alcoholic fatty liver disease. J Hepatol. 2018;69:1349–56.
13. Kwak JH, Jun DW, Lee SM, Cho YK, Lee KN, Lee HL, et al. Lifestyle predictors of obese and non-obese patients with non-alcoholic fatty liver disease: a cross-sectional study. Clin Nutr. 2018;37:1550–7.
14. Srikanthan P, Hevener AL, Karlamangla AS. Sarcopenia exacerbates obesity-associated insulin resistance and dysglycemia: findings from the National Health and Nutrition Examination Survey III. PLoS ONE. 2010;5:e10805.
15. Vila IK, Park MK, Setijono SR, Yao Y, Kim H, Badin PM, et al. A muscle-specific UBE2O/AMPKalpha2 axis promotes insulin resistance and metabolic syndrome in obesity. JCI Insight. 2019. https://doi.org/10.1172/jci.insight.128269.