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Editorial

Fatty Liver Disease and Cardiovascular Risk: Impact of Metabolic Dysfunctions

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See "Metabolic Dysfunction-Associated Fatty Liver Disease Better Predicts Incident Cardiovascular Disease" by Seogsong Jeong, et al. on page 589, Vol. 16, No. 4, 2022

Nonalcoholic fatty liver disease (NAFLD) is a heterogeneous disorder with a common phenotypic manifestation in the liver as to accumulation of excessive fatty change.[1] The diagnosis of NAFLD requires demonstration of hepatic steatosis without excessive alcohol intake and absence of other liver diseases,[2] although primary drivers and their modifiers of excessive fat deposition may vary. Meanwhile, NAFLD has been recognized as the leading cause of chronic liver disease in many regions of the world with a prevalence of up to 30%.[3] Furthermore, mortality among patients with NAFLD is reported to be significantly increased compared with the expected mortality of the general population of the same age and sex.[4] The impact of NAFLD on clinical and economic burden to the society is rising, such that the estimated annual medical costs attributable to NAFLD exceed $100 billion in the United States.[3] However, besides the lifestyle modifications, definitive pharmacotherapy is not available yet and clinical studies over new compounds have fallen short of meeting the required endpoints. This lack of effective medical treatment may be due to the heterogeneity of the population with NAFLD, and controversies over the nomenclature of NAFLD on how to reflect the complex interactions of disease driving factors persist. Recently, a panel of international experts proposed a new term, metabolic dysfunction-associated fatty liver disease (MAFLD) which requires the presence of metabolic risk factors in the setting of hepatic steatosis.[5] This shift of terminology from NAFLD to MAFLD may result in a shift of the phenotypic characteristics of individuals who meet the criteria.[6] Although most individuals with hepatic steatosis meet the criteria for both NAFLD and MAFLD, some individuals may be included on either NAFLD or MAFLD only.[6-8] Studies on this discordant groups would demonstrate the importance of metabolic factors in the prognosis of fatty liver disease.

From the Minnesota cohort study, mortality was significantly increased among the patients with NAFLD when ischemic heart disease was one of the two most common causes of death.[4] On the contrary, a recent large European study reported that NAFLD was weakly associated with cardiovascular risk[9] and another study reported that MAFLD was related with a higher risk of cardiovascular events than NAFLD.[7] Furthermore, a nationwide cohort study from the United States reported lack of association between NAFLD and increased cardiovascular mortality.[10] Regarding MAFLD in this particular study, the association was noticed between MAFLD and cardiovascular mortality although this became insignificant after adjusting for metabolic factors.

In this issue of *Gut and Liver*, Jeong *et al.*[11] present the importance of metabolic factors in fatty liver disease on predicting incident cardiovascular disease. Using a nationwide cohort from the Korean National Health Insurance Service database, including approximately 500,000 subjects, risk for cardiovascular disease shows significant increase in NAFLD with two or more factors of metabolic dysfunction with adjusted hazard ratio of 1.71. On the other hand, NAFLD patients with one or no metabolic dysfunction were not associated with increased cardiovascular disease. By definition, NAFLD with two or more metabolic

abnormalities can be classified as having both NAFLD and MAFLD, and as other previous reports, majority of NAFLD patients (90.5% in this study) were included in both NAFLD and MAFLD criteria. NAFLD patients without metabolic abnormalities and classified as NAFLD only group are only 1.65%. Although study demonstrated that NAFLD with single metabolic abnormalities did not show increased cardiovascular risk, the study did not specify details of the metabolic dysfunction. Previous studies suggest power of impaired fasting glucose on prognosis of fatty liver disease. Abnormal fasting glucose level was stated as a significant risk factor for increased mortality in NAFLD patients.[4] Definition of MAFLD also suggests diabetes as a key metabolic dysfunction so that having diabetes with fatty liver itself can be diagnosed as MAFLD. It would have been interesting to investigate metabolic factors and their influence on fatty liver in terms of natural history and disease prognosis. Comparable with this study another nationwide cohort study from South Korea also reported that those included in both NAFLD and MAFLD groups showed more increased cardiovascular disease risk than NAFLD without metabolic abnormalities.[7] However, unlike the study by Jeong *et al.*[11] which demonstrates no significant cardiovascular risk increase in NAFLD patients with fewer than two metabolic dysfunctions, this other study still suggests significant cardiovascular risk increase in NAFLD patients without metabolic abnormalities. Cardiovascular risk in association with phenotypical hepatic fatty changes independent of coexisting metabolic abnormalities would need further investigations. Nevertheless, both studies strongly suggest the trend toward increased cardiovascular risks with having multiple metabolic dysfunctions in fatty liver disease patients.

We are beginning to realize the heterogeneity of the population with fatty liver disease with respect to its primary drivers and coexisting modifiers. Although there are multiple evidences on the link between fatty liver disease and metabolic dysregulation, detailed weight of the metabolic factors on disease pathogenesis and progression still need to be investigated. More understanding of the differences might lead to the tailed treatment of fatty liver disease and related complications.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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REFERENCES

1. Schaffner F, Thaler H. Nonalcoholic fatty liver disease. Prog Liver Dis 1986;8:283-298.
2. Kang SH, Lee HW, Yoo JJ, et al. KASL clinical practice guidelines: management of nonalcoholic fatty liver disease. Clin Mol Hepatol 2021;27:363-401
3. Younossi ZM, Blissett D, Blissett R, et al. The economic and clinical burden of nonalcoholic fatty liver disease in the United States and Europe. Hepatology 2016;64:1577-1586.
4. Adams LA, Lymp JF, St Sauver J, et al. The natural history of nonalcoholic fatty liver disease: a population-based cohort study. Gastroenterology 2005;129:113-121.
5. Eslam M, Sanyal AJ, George J; International Consensus Panel. MAFLD: a consensus-driven proposed nomenclature for metabolic associated fatty liver disease. Gastroenterology 2020;158:1999-2014.
6. Wong VW, Wong GL, Woo J, et al. Impact of the new definition of metabolic associated fatty liver disease on the epidemiology of the disease. Clin Gastroenterol Hepatol 2021;19:2161-2171.
7. Lee H, Lee YH, Kim SU, Kim HC. Metabolic dysfunction-associated fatty liver disease and incident cardiovascular disease risk: a nationwide cohort study. Clin Gastroenterol Hepatol 2021;19:2138-2147.
8. Huang SC, Su HJ, Kao JH, et al. Clinical and histologic features of patients with biopsy-proven metabolic dysfunction-associated fatty liver disease. Gut Liver 2021;15:451-458.
9. Alexander M, Loomis AK, van der Lei J, et al. Non-alcoholic fatty liver disease and risk of incident acute myocardial infarction and stroke: findings from matched cohort study of 18 million European adults. BMJ 2019;367:l5367.
10. Kim D, Konyn P, Sandhu KK, Dennis BB, Cheung AC, Ahmed A. Metabolic dysfunction-associated fatty liver disease is associated with increased all-cause mortality in the United States. J Hepatol 2021;75:1284-1291.
11. Jeong S, Oh YH, Choi S, et al. Metabolic dysfunction-associated fatty liver disease better predicts incident cardiovascular disease. Gut Liver 2022;16:589-598.