pISSN 2287-2728
eISSN 2287-285X

CLINICAL and MOLECULAR HEPATOLOGY

https://doi.org/10.3350/cmh.2022.0398
Clinical and Molecular Hepatology 2023;29(Suppl):S79-S85

Review

Risk factors in nonalcoholic fatty liver disease

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Nonalcoholic fatty liver disease (NAFLD) is the most common liver disease, with a global prevalence estimated at approximately 25%. NAFLD is also the leading cause of liver cirrhosis, hepatocellular carcinoma, and death. Additionally, the risk of cardiovascular disease increases with greater NAFLD severity. The liver- and cardiovascular disease-related mortality incident rate ratios among the NAFLD population were 0.77 and 4.79 per 1,000 person-years, respectively. We intend to discuss the risk factors associated with NAFLD in terms of development and progression. Obesity or higher body mass index is closely associated with NAFLD in a dose-dependent manner, but growing evidence suggests that central obesity plays a more important role in the development of NAFLD. Saturated fat and fructose have been reported to be closely related to NAFLD. Fructose intake promotes lipogenesis and impairs mitochondria fat oxidation. The presence of type 2 diabetes is the most powerful predictive risk factor for hepatic fibrosis in patients with NAFLD. Single nucleotide polymorphism is not only associated with the prevalence of NAFLD but also associated with increased liver disease mortality. Obstructive sleep apnea, intestinal dysbiosis, and sarcopenia are associated with the development of NAFLD. **(Clin Mol Hepatol 2023;29(Suppl):S79-S85)**

Keywords: Nonalcoholic fatty liver disease; Obesity; Diabetes mellitus, type 2; Sarcopenia

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is the most common liver disease, with a global prevalence of approximately 25%.[1,2] NAFLD is an umbrella terminology incorporating a spectrum of liver diseases ranging from simple steatosis (nonalcoholic fatty liver), steatohepatitis (nonalcoholic steatohepatitis, NASH), and cirrhosis.[3] NAFLD is also the leading cause of liver cirrhosis, hepatocellular carcinoma and death.[1] A study has forecasted that the burden of NAFLD is bound to rise through 2015–2030 with elevated prevalence and mortality.[4] For example, prevalence of NAFLD was approximately 25.8% in all ages in 2015 and would reach 28.4% in 2030, respectively. Moreover, the mortality of the NAFLD population is expected to increase by 23% by 2030, accounting for 13% of all deaths.[5] Patients with NAFLD have a higher risk of liver-related mortality, but cardiovascular disease is the leading cause of death with a 1.5-fold increase.[6,7] Additionally, the risk of cardiovascular disease increases with greater NAFLD severity (odds ratio [OR] 2.58).[8] The liver- and cardiovascular

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Editor: Han Ah Lee, Korea University College of Medicine, Korea

Received : Nov. 14, 2022 / **Revised :** Dec. 11, 2022 / **Accepted :** Dec. 12, 2022

disease-related mortality incident rate ratios among the NAFLD population were 0.77 and 4.79 per 1,000 person-years, respectively.[9] Another notable cause of death in patients with NAFLD is neoplasms.[9-11] The overall cancer incidence is 1.3 times higher in patients with NAFLD than in controls (hazard ratio: 1.32, $P<0.001$).[11] Hepatocellular carcinoma and other gastrointestinal cancers, such as colorectal or stomach cancer, and breast cancer in women are the most prevalent neoplasms associated with the NAFLD population.[9,11,12] We intend to discuss the risk factors associated with NAFLD in terms of development and progression.

OBESITY AND CENTRAL OBESITY

Obesity or higher body mass index is closely associated with NAFLD in a dose-dependent manner, with approximately 20% increase in the risk of developing NAFLD for every unit increase in body mass index.[13] Furthermore, childhood obesity is also associated with fatty liver and a higher mortality overall.[14] Children with NAFLD show a 5.88-fold higher rate of all-cause mortality, including causes, such as cancer (hazard ratio 1.67 vs. 0.07/1,000 person-years), cardiometabolic disease (hazard ratio 1.12 vs. 0.14/1,000 person-years), and liver disease (hazard ratio 0.93 vs. 0.04/1,000 person-years) than the control group.[14] A retrospective cohort study has contributed to the association of central obesity and NASH and advanced fibrosis among lean patients with NAFLD.[15] In addition, both lean (OR 5.8; $P=0.004$) and overweight or obese (OR 4.2; $P=0.0001$) patients with NAFLD with central obesity (>102 cm for men, >88 cm for women) were closely associated with significant hepatic fibrosis.[15] Metaregression analysis of this cohort (n=11,400) found that waist circumference affects altered metabolic syndrome-related factors and fasting plasma glucose levels (slope: 1.55, $P=0.14$). Most studies focus on the relationship between obesity and NAFLD risk, as measured by body mass index. However, growing evidence suggests that central obesity, defined as waist circumference or waist-to-hip ratio, plays a more important role in NAFLD development.[16]

DIET

The total caloric intake is significantly higher among patients with NAFLD, but there is no significant difference in the pattern of consumption of macronutrients (e.g., proteins, fat, and carbohydrates) or micronutrients (e.g., vitamins, iron, or zinc) between the control and the NAFLD groups.[17] However, several food components, such as saturated fat and fructose, have been reported to be closely related to NAFLD development.[18] Fructose intake promotes lipogenesis and impairs mitochondrial fat oxidation, leading to increased uric acid production and depletion of adenosine triphosphate in the mitochondria, which triggers a series of reactions, such as oxidative stress.[19,20] Moreover, fructose metabolism may also affect intestinal permeability and dysbiosis, leading to the pathogenesis of NAFLD.[21] However, using Rotterdam cohort, Alferink et al.[22] could not confirm the association between NAFLD and monosaccharides and disaccharides.

TYPE 2 DIABETES MELLITUS (T2DM)

The estimated global prevalence of NAFLD, NASH and advanced hepatic fibrosis among patients with T2DM is 55.48%, 37.33%, and 17.02%, respectively (Table 1).[23] The prediabetes/diabetes status among patients with NAFLD is related to an increment in risk of severe hepatic steatosis (OR 2.00, $P<0.005$), severe lobular inflammation (OR 2.25, $P<0.005$), hepatic ballooning (OR 1.54, $P=0.069$), and significant fibrosis (OR 1.30, $P=0.45$).[24] The proportion of definite NASH is higher in patients with prediabetes/diabetes status than those with normal glucose tolerance (48.4% vs. 29.9%; $P<0.001$).[24,25] The proportion of patients with both the significant and advanced fibrosis in the T2DM group was 17.9%, whereas in the nondiabetic control group, it was 4.9% and 1.8%, respectively.[26] The findings strongly suggest that T2DM alone was an independent risk factor for hepatic fibrosis.[15] Moreover, presence of T2DM is the most powerful predictive risk factor for hepatic fibrosis even in lean patients with NAFLD.[26]

Abbreviations:

IR, insulin resistance; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; OR, odds ratio; OSA, obstructive sleep apnea; PNPLA3, patatin-like phospholipase domain-containing 3; T2DM, type 2 diabetes mellitus

https://doi.org/10.3350/cmh.2022.0398

Table 1. Prevalence of NAFLD among patients with type 2 diabetes compared to the control group

Studies	Prevalence of NAFLD, NASH, and fibrosis among T2DM		
	NAFLD	NASH	Advanced fibrosis
Younossi et al.[23] (2019)*	55.48%	37.33%	17.02%
	Analyzed 80 studies, 49,419 patients	Analyzed 10 studies, 892 patients	Analyzed 7 studies, 439 patients
Le et al.[27] (2019)	72%	2.82% (2003–2006), 5.20% (2011–2014)	0.30% (2003–2006), 0.34% (2011–2014)
	Total 3,691 patients	"NAFLD-associated advanced fibrosis", APRI score >1	"NASH-cirrhosis", APRI score >2
Kwok et al.[28] (2016)	72.8%	-	17.1%
	1,799 patients with CAP measurement	-	1,770 patients with LSM measurement

NAFLD, nonalcoholic fatty liver disease; CAP, controlled attenuation parameter; LSM, liver stiffness measurement; T2DM, type 2 diabetes mellitus; APRI, aspartate aminotransferase/platelet ratio index.
*Majority of NAFLD diagnosed by radiologic imaging techniques like ultrasound and proton magnetic resonance spectroscopy, whereas nonalcoholic steatohepatitis (NASH) and advanced fibrosis were diagnosed using liver biopsy.

GENETIC POLYMORPHISMS

The pathogenesis of NAFLD or NASH is complex and involves multiple-hit pathogenic factors, such as adiposity, lipotoxicity, insulin resistance or genetic variations, acting in concert.[29] Single nucleotide polymorphism is one of the essential factors to note. Moreover, ethnic diversity and genetic predisposition suggest that single nucleotide polymorphism in NAFLD plays an important role in its pathogenesis.[30] Recent genome sequencing advancements have helped determine the association between specific genetic variations and NAFLD development. The most prominent variants are patatin-like phospholipase domain-containing 3 (PNPLA3) and the transmembrane 6 superfamily member 2.[30] More recently, novel variants like 17-beta hydroxysteroid dehydrogenase 13, glucokinase regulator, or protein phosphatase 1 regulatory subunit 3B have been investigated as well.[30,31] The 17-beta hydroxysteroid dehydrogenase 13 variation is notable as its wild-type plays a protective role against liver inflammation.[30] The rs738409 C>G single nucleotide polymorphism encoding I149M variant of PNPLA3 and the rs58542926 C>T encoding E167K variant of transmembrane 6 superfamily member 2 are the most studied genetic predispositions associated with NAFLD. Three genotypes included in PNPLA3 variants are CC, GC, and GG. The proportion of each genotype differs in patients with and without NAFLD. The proportion of CC genotype, the wild-type, is the highest in those without NAFLD (30.8% vs. 60.2%), whereas GC and GG genotypes, the variants, are more common among patients with NAFLD (43.0% vs. 35.6% and 26.2% vs. 4.2%, respectively).[31] Single nucleotide polymorphisms are closely associated with NAFLD pathogenesis in lean people. A recent study found a higher frequency of the non CC allele of PNPLA3 in lean patients with NAFLD than in overweight and obese patients.[32] In addition, a greater proportion of lean patients are associated with the transmembrane 6 superfamily member 2 gene single nucleotide polymorphism variation.[15] A more important point was that PNPLA3 I148M was associated with increased liver disease mortality.[33]

OBSTRUCTIVE SLEEP APNEA (OSA)

Obesity causes OSA and NAFLD. In addition, OSA can independently affect the development and progression of NAFLD.[34] As a result of meta-analysis of 18 cross-sectional studies, the pooling OR of OSA for the presence of NAFLD was 2.01 to 2.99.[35] The development of NAFLD in patients with OSA is strongly associated with chronic intermittent hypoxia. Cyclic hypoxia and reoxygenation can induce fatty liver directly via hypoxia-inducing factor-1, and promote tissue inflammatory responses through the accumulation of free radicals and NF-kB.[36] OSA also activates the sympathetic nervous system and induces systemic inflammatory responses and vascular endothelial dysfunction. Activating the sympathetic nervous system increases platelet activity and aggre-

gation, leading to insulin resistance, dyslipidemia, and metabolic syndrome.[36]

MICROBIOME

Gut-liver axis refers to the bidirectional relationship between the microbiome in the gut and the liver, communicating via dietary, genetic, and environmental signals.[37] Disturbance of the liver-gut axis is associated with the NAFLD pathogenesis through gut barrier disruption, bacterial translocation, and subsequent hepatic inflammation response.[38] Although the underlying mechanism or direct causality of NAFLD due to an altered gut microbiome remains unclear, various theories are being explored. For example, Martinez-Gurin et al.[39] showed that NAFLD did not occur due to decreased lipid metabolism and intestinal absorption even in a high-fat diet in germ-free mouse conditions. Resistance of NAFLD in germ-free mice is explained by the inhibition of lipid metabolism via disrupted enteroendocrine signaling (e.g., CCK) and fatty acid transportation (e.g., Cd36 and Dgat1). It was confirmed that absorption of intestinal fat was increased when a high-fat diet was administered after changing the germ-free mouse to general breeding conditions. These data showed how fat absorption changes according to the intestinal microflora's condition.

SARCOPENIA

Sarcopenia is defined as a progressive loss of muscle mass and its strength, more prevalent in patients with chronic medical conditions, such as chronic obstructive pulmonary disease, chronic kidney disease, or NAFLD, than in the healthy population.[40-43] Sarcopenia and NAFLD are associated in a bidirectional manner,[44] independent of insulin resistance (IR) or obesity[41] because they share common pathophysiological mechanisms.[40] It is also suggested that sarcopenia is associated with worse clinical outcomes in general.[43,45] Skeletal muscle plays a central role in glucose metabolism as one of the largest organs in our body to utilize glucose. Loss of muscle mass due to aging,[45] nutrient deficiency, or lack of physical activity leads to weaker muscle strength and dysregulated metabolic function. Skeletal muscle is one of the most significant insulin-stimulated sites in the body, which is generally considered the main culprit of IR.[46] A vicious cycle of local myosteatosis and muscle IR plays a major role in creating systemic inflammation and IR. This vicious loop, called the "metabaging cycle", comprises lipid metabolism dysfunction, lipotoxicity, IR, local inflammation, and lipolysis. Proinflammatory factors involved in the cycle, such as interleukin-6, and tumor necrosis factor-alpha, further induce secretion of cytokines positively, gradually spreading local inflammation into a systemic issue.[47] IR and chronic inflammatory status are common comorbidities among patients with NAFLD, including dysregulation of lipid metabolism.[48,49] Hong et al.[40] suggested that NAFLD and sarcopenia are negatively correlated with homeostasis model assessment of IR and high-sensitivity C-reactive protein. In addition, Koo et al.[42] showed that the prevalence of sarcopenia in patients with NAFLD was higher than in the control group (17.9% vs. 8.7%, $P<0.001$). The risk of NASH and significant fibrosis with sarcopenia is 2.30 and 2.05 times higher than the control group, respectively. The prevalence of significant fibrosis (≥F2) is higher in patients with sarcopenia than those without (OR 2.01, 45.7% vs. 24.7%; $P<0.001$).[42] Moreover, there was a higher prevalence of Child-Pugh class C cirrhosis than those with class B or A in patients with sarcopenia (46.7% vs. 37.9% vs. 23.3%, respectively; $P=0.007$).[50] It is also associated with a higher prevalence of cirrhosis-related complications (81.82% vs. 62.24%, $P<0.001$).[45] The overall survival rate seems significantly lower (relative risk 2.64) than cirrhosis without sarcopenia. It suggests the association of cirrhotic complications, such as ascites (relative risk of 1.82), spontaneous bacterial peritonitis (relative risk of 3.33), hepatic encephalopathy (relative risk of 1.96), and upper gastrointestinal varices (relative risk of 2.13).[45] Five-year survival probabilities of patients with cirrhosis and sarcopenia was shorter than those without (46.6% vs. 74.2%, $P<0.001$).[50]

Authors' contribution

Drafting the article, Eunji Ko; Critical revision of the article, Eileen L. Yoon and Dae Won Jun.

Acknowledgements

This research was supported by grants from the National Research Foundation of Korea 2020R1A2C2009227.

https://doi.org/10.3350/cmh.2022.0398

Conflicts of Interest

The authors have no conflicts to disclose.

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