

Recent Epidemiology and Risk Factors of Nonalcoholic Fatty Liver Disease

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Because of the global obesity epidemic, the incidence and prevalence of nonalcoholic fatty liver disease (NAFLD) have increased worldwide, including among Koreans. Recently, the incidence rate of NAFLD in Korea was reported to be 45.1 per 1,000 person-years, and the prevalence as approximately 30% depending on the diagnostic methods used. The incidence of advanced fibrosis and hepatocellular carcinoma, as well as all-cause and liver-related mortality in NAFLD patients has increased substantially, imposing considerable public health costs in Korea. Genetic, demographic, environmental, and clinical factors are involved in the pathogenesis of NAFLD. Some genetic variants, such as patatin-like phospholipase domain-containing 3 (*PNPLA-3*) and sorting and assembly machinery component 50 (*SAMM-50*), play a major role in the occurrence of NAFLD. The risk of NAFLD and fibrosis increases with advancing age and in men. Nutritional factors, inadequate exercise, and sleep duration are also associated with increased risk of NAFLD. Obesity is a major risk factor for NAFLD; however, NAFLD in lean individuals has been noted in recent studies. Insulin resistance, type 2 diabetes, and metabolic syndrome and its components are closely associated with NAFLD development and liver fibrosis with various underlying mechanisms. Sarcopenia likely shares a common pathophysiology with NAFLD. The rapidly increasing incidence and prevalence of NAFLD and its complications, as well as the associated healthcare burden, warrant early assessment of NAFLD and its risk factors to prevent NAFLD-related complications in high risk groups.

Key words: Nonalcoholic fatty liver disease, Epidemiology, Incidence, Prevalence, Risk factor

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INTRODUCTION

The global epidemics of obesity and type 2 diabetes have led to a dramatic increase in the prevalence of nonalcoholic fatty liver disease (NAFLD) both in Korea and worldwide.¹ Recently, NAFLD has been reported to afflict more than 25% of the general population worldwide, and the prevalence has been estimated to be up to

30% in Korea.¹ As the incidence of obesity and type 2 diabetes is predicted to rise rapidly due to westernized lifestyles, NAFLD is also expected to increase in the future. NAFLD is a major cause of chronic liver disease. The spectrum of disease severity of NAFLD ranges from simple steatosis and nonalcoholic steatohepatitis (NASH) to its complications such as cirrhosis, end-stage chronic liver disease, and hepatocellular carcinoma (HCC).² The patho-

genesis of NAFLD varies and is complex including genetic, environmental factors, and clinical factors such as metabolic syndrome and its components.³ Nonetheless, the distinct classification of NAFLD and the treatment options to directly resolve NAFLD are still lacking.^{3,4} This review sought to explore recent trends in the epidemiology of NAFLD and emerging risk factors, which may be cornerstones for prevention and better management of NAFLD.

EPIDEMIOLOGY OF NAFLD

Incidence of NAFLD

Table 1 presents the incidence and prevalence of NAFLD. The incidence of NAFLD shows an increasing trend worldwide. According to a cohort study in the United States, the age- and sex-adjusted incidence of NAFLD increased from 62 per 100,000 person-years in 1997 to 329 per 100,000 person-years in 2014.^{5,6} A meta-analysis in 2016 based on studies between 1989 and 2015 showed that the pooled regional incidence of NAFLD was 52.34 per 1,000 person-years (95% confidence interval [CI], 28.31–96.77) in Asia, and 28.01 per 1,000 person-years (95% CI, 19.34–40.57) in Israel, respectively.⁷ According to a recent meta-analysis on observational studies in Asia from 1999 to 2019, the overall pooled annual incidence rate of NAFLD was 50.9 per 1,000 person-years (95% CI, 44.8–57.4), and the incidence rate in South Korea was 45.1 per 1,000 person-years (95% CI, 37.9–52.9).⁷

Table 1. Incidence and prevalence of nonalcoholic fatty liver disease

Variable	Incidence (95% CI)	Prevalence, % (95% CI)*
Global ⁷	-	25.24 (22.10–28.65)
North America ⁷	-	24.13 (19.73–29.15)
United States ^{5,6}	329 [†]	37.50 (34.00–41.00) [†]
South America ⁷	-	30.45 (22.74–39.44)
Europe ⁷	-	23.71 (16.12–33.45)
Africa ⁷	-	13.48 (5.69–28.69)
Asia ^{7,9}	50.9 (44.8–57.4) [‡]	27.37 (23.29–31.88)
South Korea ⁹	45.1 (37.9–52.9) [‡]	32.87 (31.12–34.67)
China (mainland) ⁹	63.0 (47.0–81.3) [‡]	29.81 (27.78–31.93)
Japan ⁹	29.0 (26.3–31.7) [‡]	22.28 (18.69–26.34)

*Prevalence (%) was based on nonalcoholic fatty liver disease diagnosis using imaging techniques; [†]Prevalence (%) was based on nonalcoholic fatty liver disease diagnosis using imaging technique and liver biopsy data; [‡]Incidence per 100,000 person-year; [§]Incidence per 1,000 person-year. CI, confidence interval.

Prevalence of NAFLD

The prevalence of NAFLD varies depending on the study subject, definition, and diagnostic methods, which usually include radiological, laboratory, and histological examinations. In a meta-analysis in 2016, the estimated global prevalence of NAFLD diagnosed by imaging techniques (ultrasound, computed tomography, and magnetic resonance imaging [MRI]/spectroscopy) was 25.24% (95% CI, 22.10–28.65). After stratified analysis by region, the prevalence in Europe and North America was 23.71% (95% CI, 16.12–33.45) and 24.13% (95% CI, 19.73–29.15), respectively; whereas, the prevalence in Asia was 27.37% (95% CI, 23.29–31.88).⁷ In a large middle-aged U.S. cohort study, the prevalence of NAFLD was 37.5% (95% CI, 34–41) using by MRI based LiverMultiScan[®] proton density fat fraction (LMS-PDFF) and liver biopsy data.⁸ According to another meta-analysis in Asia, the overall prevalence of NAFLD was 29.62% (95% CI, 28.13–31.15) regardless of diagnostic method; among these, the prevalence diagnosed by ultrasound was 30.55% (95% CI, 29.26%–31.86%).⁹ In the same study, the prevalence of NAFLD in South Korea was 32.87% (95% CI, 31.12%–34.67%), and the prevalence in China and Japan was 29.81% (95% CI, 27.78%–31.93%) and 22.28% (95% CI, 18.69%–26.34%), respectively. As suggested above, the prevalence of NAFLD in Asian countries was estimated to be similar to, and in some cases, higher than in western nations. Meanwhile, the prevalence of NAFLD in Asia diagnosed based on fatty liver index or hepatic steatosis index was estimated to be 15.82% (95% CI, 13.18%–18.89%).⁹ In a cross-sectional study in South Korea, the prevalence of NAFLD diagnosed by transient elastography was 42.9%, and 5% of NAFLD patients had significant fibrosis.¹⁰

In the case of children and adolescents, the prevalence of NAFLD is also increasing with rising childhood obesity. Based on the National Health and Nutrition Examination Survey conducted between 2015 and 2017, when NAFLD was diagnosed based on blood tests, the prevalence was estimated to be 11.2% (14.7% for boys and 7.4% for girls), which was higher than the 7.8% value obtained in 2001–2005 (10.6% for boys and 4.6% for girls).¹¹ Considering that 40%–45% of obese adolescents have NAFLD,¹² it is predicted that the prevalence of NAFLD will increase rapidly along with increasing obesity among children and adolescents in Korea.¹

Disease progression in NAFLD

Global epidemiologic studies have shown that NAFLD can progress to liver cirrhosis (LC) or HCC, although the exact burden of NAFLD-associated LC and HCC remains unclear. In relation to the natural course of NAFLD, the incidence of NASH has been reported to vary depending on the follow-up period and diagnostic criteria. In a population-based study of U.S. adults, the prevalence of NAFLD-related advanced fibrosis based on noninvasive markers significantly increased between 2005 and 2016: from 2.6% (2005–2008) to 4.4% (2009–2012) to 5.0% (2013–2016) when diagnosed by the hepatic steatosis index; and from 3.3% (2005–2008) to 6.4% (2009–2012) to 6.8% (2013–2016) when diagnosed by U.S. Fatty Liver Index ($P < 0.01$).¹³ A meta-analysis reported that 132 (36.1%) of 366 biopsy-proven NAFLD patients developed progressive fibrosis.¹⁴

The annual incidence of HCC in NAFLD patients was 0.44 per 1,000 person-years (95% CI, 0.29–0.66).⁶ The incidence of HCC due to NAFLD is also on the rise. A study of the U.S. population showed that NAFLD was a common etiology of HCC (59%), and data from the Scientific Registry of Transplant Recipients from 2002 to 2017 showed that the prevalence of HCC in NASH increased by 11.5-fold, and that HCC-induced liver transplantation increased 8.5-fold in the United States.^{5,15–17}

Disease burden in NAFLD

NAFLD and its complications cause a considerable healthcare burden worldwide. In the United States, the hospitalization rate due to NAFLD-related decompensated cirrhosis has increased 10.6% annually, from 13.4 per 100,000 hospitalizations to 32.1 per 100,000 hospitalizations. Hospitalization for NAFLD-related HCC showed an 8% increase in annual rate.¹⁸

When nonalcoholic fatty liver (K75.8) was analyzed using Korea National Health Insurance Database data, the number of patients treated steadily increased every year from 24,379 patients in 2013 to 51,256 in 2017, an average annual increase of 21%. In addition, total domestic medical expenses for NAFLD increased from 4.72 billion won in 2013 to 10.53 billion won in 2017, representing an average annual increase of 22.7%. The total cost of inpatient and outpatient treatment increased by a mean of 27.4% and 23.2% annually, respectively.¹⁹

Mortality in NAFLD

Several studies explored all-cause mortality due to NAFLD. According to a meta-analysis of cohort studies on NAFLD, pooled liver-specific and overall mortality rates were 0.77 per 1,000 person-years (95% CI, 0.33–1.77) and 15.44 per 1,000 person-years (95% CI, 11.72–20.34), respectively.⁷ According to a meta-analysis in 2019 based on observational studies, risk of all-cause death (hazard ratio [HR], 1.34; 95% CI, 1.17–1.54, with substantial heterogeneity) and death from liver disease (HR, 2.53; 95% CI, 1.23–5.18, with substantial heterogeneity) were higher in patients with NAFLD. In this study, there was no significant association of NAFLD with risk of death from cardiovascular diseases (CVD; HR, 1.13; 95% CI, 0.92–1.38, with moderate heterogeneity) or death from cancers (HR, 1.05; 95% CI, 0.89–1.25, with low heterogeneity).²⁰ In the same meta-analysis, the annual mortality rate in the patients with NAFLD was 5.3 per 1,000 person-years (95% CI, 1.5–11.4) in Asia, and 1.1 per 1,000 person-years (95% CI, 1.0–1.2) in South Korea. Among these studies with Asians included in this meta-analysis, CVD-related mortality rates ranged from 0.42 to 1.1 per 1,000 person-years, and liver-related mortality rates ranged from 0.2 to 1.25 per 1,000 person-years.⁹ Although the association between NAFLD and mortality has not yet been clearly established, several studies have shown an increase in mortality, but it is difficult to draw firm conclusions because NAFLD itself includes various states depending on disease progression.

RISK FACTORS OF NAFLD

Genetic predisposition

Certain genetic variants play a major role in the occurrence and severity of NAFLD. Patatin-like phospholipase domain-containing 3 (*PNPLA-3*) and transmembrane 6 superfamily, member 2 (*TM6SF2*) single-nucleotide polymorphisms affect the development and progression of the NAFLD.^{21,22} One meta-analysis study showed that *PNPLA-3* exerted not only 73% higher liver fat accumulation but also more aggressive disease.²³ Specifically, *PNPLA-3* and sorting and assembly machinery component 50 (*SAMM-50*) were involved in the occurrence and severity of NAFLD in Korea.²⁴ In addition, farnesyl diphosphate farnesyl transferase I (*FDFT1*) is associated with increased severity of NAFLD activity, collagen type

XIII alpha 1 (*COL13A1*) is associated with the increased severity of fibrosis, and neurocan (*NCAN*) and glucokinase regulatory protein (*GCKR*) are associated with increased risk of hepatic steatosis.²⁵ A recent study showed that sterol regulatory element binding transcription factor 2 (*SREBF2*) rs133291, membrane bound O-acyltransferase domain-containing 7 transmembrane channel-like 4 (*MBOAT7-TMC4*) rs641738, and 17 β -hydroxysteroid dehydrogenase type 13 (*HSD17B13*) rs72613567 are associated with increased risk of NASH.²⁶

Sex and age

The prevalence of NAFLD is generally higher in men than in women.²⁷⁻²⁹ The prevalence of NAFLD in men tends to increase in middle-aged individuals and then decrease after the age of 50, following an inverted U-shaped curve.^{28,29} The prevalence in women is lower before the age of 50 and increases after post-menopause, reaching a peak at the age of 60.^{28,29} Men have a higher risk of more severe liver fibrosis compared to premenopausal women.³⁰ However, post-menopausal women have a similar risk of severe liver fibrosis as in men, suggesting that estrogen may be protective against fibrogenesis.³⁰ The risk of NAFLD increases with advancing age because the prevalence of risk factors, such as metabolic syndrome, type 2 diabetes, and hypertension also rises.³¹ In addition, one study showed that advancing age is a risk factor for severe liver fibrosis in patients with NASH.³¹

Race/ethnicity

Hispanics have the greatest prevalence of NAFLD followed by Caucasians and African Americans, despite African Americans having the highest prevalence of obesity and metabolic syndrome.³² This is likely due to genetic predisposition. The *I148M* variant of *PLPLA3*, which is associated with liver fat accumulation and NAFLD, had the highest prevalence among Hispanic Americans, followed by non-Hispanic whites, Asian Americans, and non-Hispanic blacks.³³ Another study showed that the prevalence of *I148M* and NAFLD was increased in Indian Asians.³⁴

Diet

Some nutritional factors contribute to the occurrence of NAFLD. Fructose, either from sucrose or high fructose corn syrup

found in beverages, contributes to not only development of hepatic steatosis but promotion to NASH.³⁵ Sugars promote de novo lipogenesis and trigger an inflammatory response leading to hepatocyte apoptosis through the c-Jun-N-Terminal pathway.³⁶ Omega-3 fatty acids reduces hepatic fat accumulation in NAFLD. A meta-analysis including 10 randomized controlled trials showed omega-3 fatty acids to be effective in reducing hepatic fat content in patients with NAFLD and NASH.³⁷ A Mediterranean diet includes high levels of omega-3-fatty acids and antioxidants. One study including 584 patients showed that a Mediterranean diet reduces insulin resistance and NAFLD.³⁸ Therefore, some physicians recommend a Mediterranean diet for the prevention and treatment of NAFLD.³⁹

Physical activity

Lack of physical activity increases the risk of NAFLD.⁴⁰ A lower level of habitual physical activity is associated with higher intrahepatic fat content⁴⁰ and helps to normalize liver enzymes such as alanine aminotransferase among patients with NASH.⁴¹ Because exercise may influence both insulin sensitivity and circulating levels of adiponectin, the association between lower intrahepatic fat content and higher physical activity may be mediated by the effect of fitness status on insulin sensitivity and adiponectin rather than having a direct effect on liver storage.⁴² Regular aerobic exercise for 6–12 weeks was beneficial for reducing hepatic steatosis and visceral fat accumulation among adolescents with NAFLD.⁴³ However, some studies showed that short-term exercise did not affect intrahepatic fat content.⁴⁴

Sleep

Some studies showed that poor sleep quality and sleep deviation are associated with obesity,⁴⁵ which contributes to the pathogenesis of NAFLD.⁴⁶ The possible mechanism for this association has been the role of inflammatory cytokines such as interleukin 6 and tumor necrosis factor-alpha (TNF- α), which are increased by sleep disturbances. These cytokines increase adipocyte lipolysis, which in turn can cause hepatic overflow of free fatty acids.⁴⁷ In addition, lack of sleep may affect the hypothalamus-pituitary-adrenal axis and cortisol metabolism, leading to liver fat storage.⁴⁸

Gut microbiota and oxidative stress

Patients with NAFLD exhibit small intestinal bacterial overgrowth and elevated levels of TNF- α .^{49,50} One possible mechanism of injury induced by intestinal microbiota is endotoxin production, which increases the risk of hepatic steatosis.⁵¹ Oxidative stress is associated with increased risk of NAFLD. Insulin resistance can result in hyperinsulinemia, consequently blocking mitochondrial oxidation of fatty acids, which are then partially metabolized by peroxisomes and microsomes, with the subsequent production of reactive oxidation species (ROS) and lipid peroxidation.⁵² This production of ROS and lipid peroxidation can reduce antioxidant enzymes and induce hepatocytes susceptible to injury.⁵³ Conversely, antioxidants, such as vitamin E, improve in patients with steatohepatitis.⁵⁴

Obesity

The ongoing obesity epidemic has led to a significant increase in NAFLD prevalence. Obesity is an established risk factor for NAFLD and NAFLD prevalence increases as body mass index (BMI) rises. A recent meta-analysis reported that NAFLD prevalence was significantly higher in a morbidly obese group (78.09%; 95% CI, 64.37–87.55) when diagnosed using all modalities, compared with 52.65% (95% CI, 48.20%–57.05%) and 12.01% (95% CI, 10.47%–13.75%) in an overweight or obesity group and nonobese group, respectively.⁹

The prevalence of NAFLD is 50%–90% among individuals with obesity,^{7,55} and the prevalence of obesity in NAFLD is 51%.⁵⁶ Weight gain increases the risk of incident NAFLD, and weight loss is the only proven method for improvement and resolution of NAFLD.^{57,58} Abdominal obesity is associated with insulin resistance and increased hepatic fat content.⁵⁹ Visceral fat tissue releases TNF and leptin, which may increase the risk of fibrosis.⁶⁰ Recent studies have reported that visceral adiposity is associated with incident NAFLD and NAFLD-related fibrosis, while other types of abdominal fat such as subcutaneous adiposity is associated with the remission of NAFLD.⁶⁰ Although NAFLD is significantly associated with obesity, the prevalence of NAFLD in lean individuals is 5%–10% of NAFLD.²¹ Although data on the incidence rate of NAFLD in non-obese Koreans are somewhat limited, in 2004, the prevalence of NAFLD was 16.1% among 460 domestic health checkup examinees with BMI of 18.5–25 kg/m².⁶¹ Risk factors for lean NAFLD include abdominal obesity, high fructose intake, weight gain even

within normal BMI, and genetic factors.⁶² In particular, the prevalence of lean NAFLD is high in Asian populations,⁶² possibly because of the high prevalence of abdominal obesity even at normal weight among Asians.⁶³

Insulin resistance and type 2 diabetes

Insulin resistance plays an important role in the occurrence of NAFLD. It promotes lipolysis of adipose tissue, which causes the release of free fatty acids and their deposition in the liver, leading to steatohepatitis. Potential mechanisms of insulin resistance in the pathogenesis of NAFLD also include mitochondrial fatty acid oxidation, increased lipogenesis, and lower levels of adiponectin.⁶⁴ Several population-based studies reported that the prevalence of NAFLD is greater in patients with type 2 diabetes, ranging from 30% to 70%. A recent systematic review and meta-analysis showed that the overall prevalence of NAFLD was 55.5% among patients with type 2 diabetes.⁶⁵ In addition, type 2 diabetes patients are at higher risk for the possibility of NASH and liver-related complications, including cirrhosis-related mortality,⁶⁶ and face 3–5-fold higher NAFLD-related mortality than individuals without type 2 diabetes.⁶⁷ Meanwhile, type 2 diabetes and NAFLD appear to affect each other. The prevalence of diabetes was significantly higher in NAFLD patients than a control group, and the incidence and prevalence of type 2 diabetes increased as hepatic fibrosis progressed.⁶⁸⁻⁷⁰ Recent studies revealed that NAFLD is associated with CVD risk, which is closely related to type 2 diabetes due to macrovascular complications; moreover, microvascular complications of type 2 diabetes are also prevalent in NAFLD patients. The presence of NASH may be affected by the treatment of type 2 diabetes.⁷¹ Growing evidence has shown that anti-diabetic medications may have beneficial effects in NAFLD/NASH. Several studies showed that pioglitazone or liraglutide improves metabolic or histological derangements in patients with NASH.⁷² The American Association for the Study of Liver Diseases recommended the pioglitazone could be used in patients with histologically proven NASH.⁷³

Dyslipidemia

Lipotoxicity refers to a high level of toxic lipids and derivatives caused by fat content accumulation in non-adipose tissues, which

activates inflammatory pathways, cellular dysfunction, and lipopapoptosis among NAFLD patients.⁷⁴ Lipotoxicity plays a key role in the progression of mild NAFLD to steatohepatitis. Therefore, NAFLD patients have higher levels of triglycerides, free fatty acids, and other lipid types such as bile acids, free cholesterol, lysophosphatidylcholines, and ceramides.⁷⁵ Hypertriglyceridemia is an independent predictor of NAFLD and also increases the risk of cirrhosis.⁷⁶ Studies reported that fatty liver is significantly associated with a higher prevalence of hypertriglyceridemia and low high-density lipoprotein (HDL) cholesterol; NASH was associated with higher levels of non-HDL cholesterol.^{77,78} Hepatocytes release proprotein convertase subtilisin/kexin type 9 (PCSK9), which inhibits the uptake of low-density lipoproteins. PCSK9 level is related to the degree of steatosis and increases with hepatic fat accumulation.⁵¹ Some studies have shown that several lipid-lowering medications are effective for improving the histological features of NASH.⁷⁹ In particular, statins have been shown to reduce the progression of hepatic fibrosis, the possibility of hepatic decompensation, and the risk of all-cause death in patients with chronic liver disease.⁷⁹ Statins have also been reported to have anti-cancer properties that may reduce the risk of HCC.⁸⁰

Metabolic syndrome

Metabolic syndrome comprises abdominal obesity, hypertriglyceridemia, low HDL cholesterol, hyperglycemia, and high blood pressure. These components of metabolic syndrome are frequently associated with NAFLD; thus, NAFLD is recognized as a hepatic manifestation of metabolic syndrome.¹⁴ The prevalence of NAFLD was 4-fold higher in individuals with metabolic syndrome than those without it,⁸¹ and moreover, the presence of multiple traits of metabolic syndrome was associated with a higher likelihood of more severe liver disease.⁸² Furthermore, a growing body of evidence has demonstrated bidirectional relationships between metabolic syndrome and NAFLD, with each disease acts as an initiating or aggravating factor for the other.¹⁴ Each component of metabolic syndrome except high blood pressure was discussed above. A meta-analysis that identified 11 studies including 411 patients with pathologically proven NAFLD found that hypertension was correlated with liver fibrosis progression.⁸³ A study of Korean men showed that the incidence of hypertension was strongly associated with more severe NAFLD than milder forms.⁸⁴ In addition, the occurrence of incident fatty liver increased the risk of hypertension among Korean middle-aged adults.^{14,85}

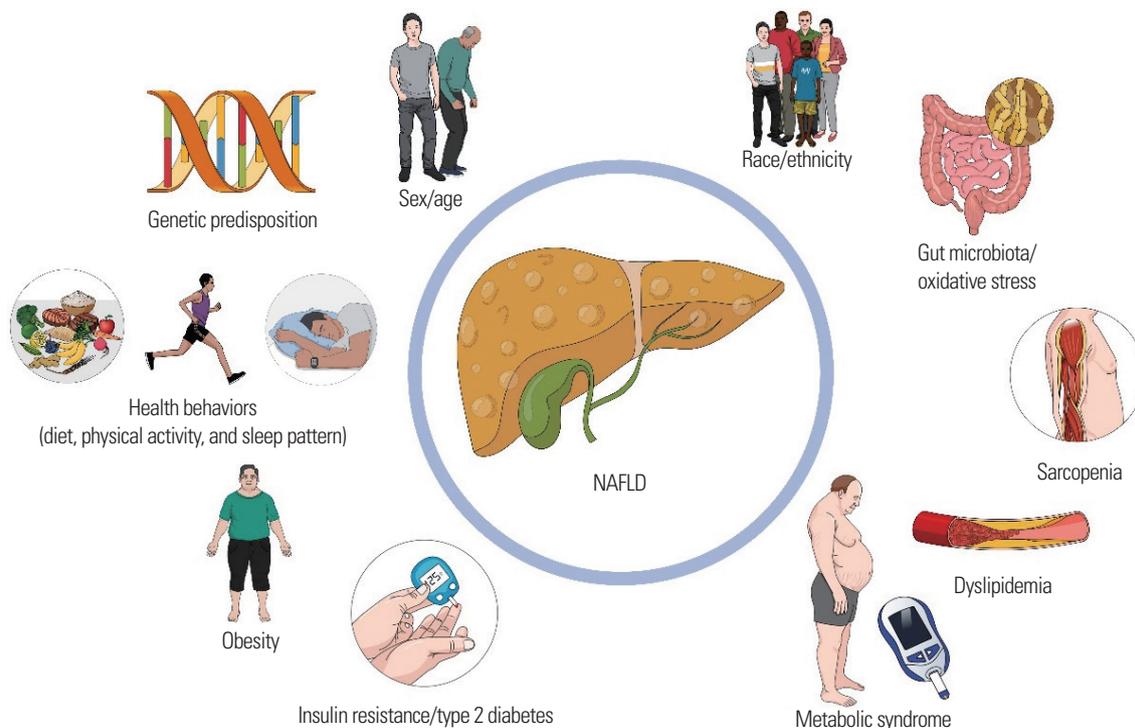


Figure 1. Risk factors of nonalcoholic fatty liver disease (NAFLD).

Sarcopenia

Sarcopenia is characterized by reduced skeletal muscle mass, strength, and function, and is usually diagnosed based on loss of appendicular muscle mass. Sarcopenia has been reported to be prevalent in patients with NAFLD/NASH (20%) and cirrhosis (40%–70%).⁸⁶ Several observational studies revealed that sarcopenia manifests in early-stage liver disease and worsens the severity of liver disease.^{87,88} Sarcopenia and NAFLD likely share common underlying mechanisms: insulin resistance, chronic inflammation, changes in growth hormone, nutritional deficiencies, and inactivity, and are interconnected through the muscle-liver-adipose tissue axis.^{89,90} Skeletal muscle plays a crucial role in the transport and disposal of glucose, oxidation of fatty liver, and energy homeostasis, which are key determinants in NAFLD pathophysiology. Myosteatosis, ectopic lipid filtration in the skeletal muscle related to increased energy intake, leads to peripheral insulin resistance and usually occurs before the development of NAFLD.⁹¹ Metabolic inflexibility followed by insulin resistance and crosstalk between target organs such as skeletal muscle, liver, and adipose tissue, are major determinants in the physiopathology and progression of both diseases.⁸⁶ We summarized the risk factors of NAFLD in Fig. 1.

CONCLUSION

NAFLD is the most common chronic liver disease with an increasing prevalence globally. Various risk factors such as genetic predisposition and health-related behaviors are associated with the incidence and progression of NAFLD. Obesity and metabolic syndrome and its components appear to be closely associated with risk of NAFLD. Recently, sarcopenia has been noted as an emerging risk factor of NAFLD, mainly in studies of Asians. Further studies are warranted to explore the epidemiology and pathophysiology underlying the relationships among emerging risk factors and NAFLD.

CONFLICTS OF INTEREST

Ga Eun Nam has worked as an Associate Editor of the journal since 2020. However, she was not involved in peer reviewer selection, evaluation, or the decision process for this article. There are no other potential conflicts of interest relevant to this article to report.

AUTHOR CONTRIBUTIONS

Study concept and design: all authors; acquisition and interpretation of data: all authors; drafting of the manuscript: all authors; critical revision of the manuscript: all authors; and study supervision: YJC and GEN.

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