Review Article

Diversity in NAFLD: A Review of Manifestations of Nonalcoholic Fatty Liver Disease in Different Ethnicities Globally

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Abstract

Globally, the rise in prevalence of obesity and metabolic syndrome as a whole has been linked to increased access to processed foods, such as refined sugars and saturated fats. Consequently, nonalcoholic fatty liver disease (NAFLD) is on the rise in both developed and developing nations. However, much is still unknown on the NAFLD phenotype with regards to the effect of ethnic diversity. Despite similarities in dietary habits, it appears that certain ethnicities are more protected against NAFLD than others. However, manifestations of the same genetic polymorphisms in different groups of people increase those individuals' predisposition to NAFLD. Diets from different regions have been associated with a lower prevalence of NAFLD and have even been linked to regression of hepatic steatosis. Socioeconomic variations amongst different regions of the world also contribute to NAFLD prevalence and associated complications. Thus, a thorough understanding of ethnic variability in NAFLD is essential to tailoring treatment recommendations to patients of different backgrounds.

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Introduction

The current landscape of liver disease has evolved over the last few decades. With the advent of highly effective therapy for viral hepatitis, nonalcoholic fatty liver disease (NAFLD) has become one of the most common etiologies of chronic liver disease.[1] NAFLD is defined by detection of hepatic steatosis, or the presence of macrovesicular fat in >5% of hepatocytes, either by imaging or histology, after exclusion of secondary causes and alcoholic fatty liver disease.[2] Currently, international experts consensus have proposed the more comprehensive and practical nomenclature of "metabolic dysfunction-associated fatty liver disease (MAFLD)", which is defined by evidence of hepatic steatosis plus one of the following three criteria: overweight/obesity, presence of type 2 diabetes mellitus (DM), or evidence of metabolic dysregulation.[3,4]

The increased prevalence of NAFLD is driven in large part by the increasing presence of metabolic syndrome, obesity, sedentary lifestyle, and improved access to food supplies globally.[5] The effect is seen not only in adults but also in children and adolescents.[6] This review will focus primarily on ethnic differences in NAFLD prevalence and its socioeconomic effect, in addition to risk factors, manifestations, diagnosis, and outcomes.

Diagnosis and manifestations

NAFLD is a spectrum of disease continuity, ranging from simple steatosis, steatohepatitis (NASH) with or without different stages of fibrosis, cirrhosis, and hepatocellular carcinoma (HCC).[7] Even though most cases of HCC develop in cirrhotic patients, there is increasing evidence of development of HCC in non-cirrhotic NASH.[8] The majority of individuals with NAFLD are asymptomatic, and the diagnosis is often discovered incidentally during workup for elevated liver function tests or via imaging for another purpose. Compared to the non-NAFLD population, a higher rate of fatigue impairing physical function has been found in NAFLD/NASH patients. Energy level is found to be lower in patients with significant hepatic fibrosis compared to a normal/mild hepatic fibrosis group.[9,10] Pruritus has also been reported among NASH patients.[11] Other symptoms include abdominal bloating/swelling, abdominal discomfort, sleep disturbance, or apnea.[12] There are no data on difference in presentations amongst various ethnicities.

NAFLD is most often diagnosed non-invasively with abdominal imaging; although, a liver biopsy is the gold standard to determine the presence steatohepatitis and stage of fibrosis. It is worth noting that ultrasound sensitivity to NAFLD is poor when steatosis occupies less than 30% of the liver, making it an inferior modality to diagnose the condition at the 5% liver fat reference.[13] However, specific biomarker panels such as the fatty liver index (FLI) as validated in Italy (AUROC 0.84)[14] and the hepatitis steatosis index (HIS) as validated in Korea (AUROC 0.81)[15] can augment ultrasonography and assist in better defining the risk of steatosis in patients of different ethnicities.

Due to the higher cost and/or health risks associated with other modalities, such as computed tomography or liver biopsy, ultrasound is primarily used to diagnose patients in

Keywords: Nonalcoholic fatty liver; Nonalcoholic steatohepatitis; Ethnicity; Diversity; Body mass index; Lean.

Abbreviations: APRI, aspartate aminotransferase/platelet ratio index; ARFI, acoustic radiation force impulses; BMI, body mass index; CAP, controlled attenuation parameter; DM, diabetes mellitus; FIB-4, fibrosis-4 index; FLI, fatty liver index; GWAS, genome-wide association studies; HCC, hepatocellular carcinoma; HIS, hepatitis steatosis index; MAFLD, metabolic dysfunction-associated fatty liver disease; MRE, magnetic resonance elastography; MS, metabolic syndrome; NAFLD, nonalcoholic fatty liver; NASH, nonalcoholic steatohepatitis; NHANES, National Health and Nutrition Examination Survey; PNPLA3, patatin-like phospholipase domain-containing protein 3; TE, transient elastography.

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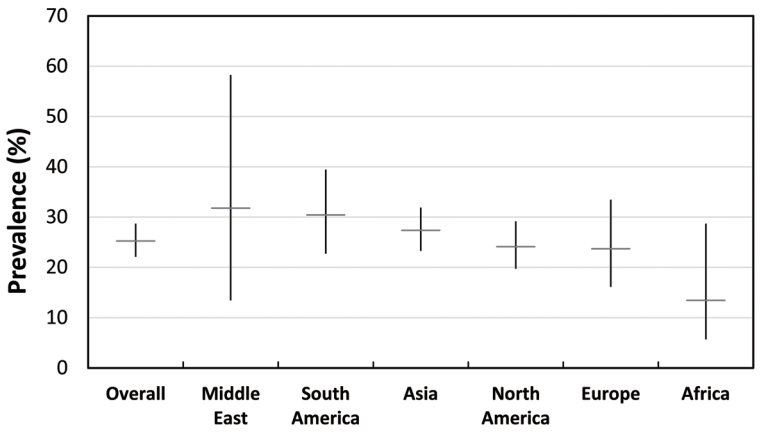

Fig. 1. Prevalence of NAFLD by geographical regions.

developing countries.[16] Controlled attenuation parameter (CAP) is an ancillary tool to conventional ultrasonography and measures how hepatic fat attenuates ultrasound waves while liver stiffness is measured by transient elastography. It can assist in detecting and grading hepatic fat, although it has not been shown to reliably estimate the quantity of liver fat.[17] Magnetic resonance imaging, *i.e.* spectroscopy or proton density fat fraction, is increasingly being used in NAFLD clinical trials to detect hepatic steatosis in both Western and Eastern countries.[18] Factors that prevent magnetic resonance imaging from consideration as a first-line diagnostic tool include accessibility due to specialized equipment parts and expertise of the operator and radiologist.[19] A noninvasive algorithm developed in Finland, known as the NAFLD liver fat score, used ^{1}H-MRS as a reference and had an AUROC of 0.86–0.87, but used serum insulin level as a part of its panel, which limited its accessibility to a wider patient population.[20]

Assessing the stage of hepatic fibrosis is important in NAFLD as it can predict the risk of disease progression and mortality.[21] Non-invasive tests including serum biomarkers and imaging tests have been developed to detect hepatic fibrosis in risk stratification. Non-invasive serum biomarkers include simple tests, such as aspartate aminotransferase/alanine aminotransferase ratio, NAFLD fibrosis score, fibrosis-4 (commonly known as FIB-4) index, and aspartate aminotransferase/platelet ratio index (commonly known as APRI), and complex tests, such as FibroTest/FibroSure, Fibrospect, enhanced liver fibrosis panel, Pro-C3 based predictive fibrosis score and NIS4, which are not commercially available yet.[22] However, the simple non-invasive biomarkers are less sensitive in identifying advanced fibrosis in South Asians compared to Caucasians.[23] The imaging tests including transient elastography, acoustic radiation force impulses (commonly known as ARFI), 2D shear wave elastography and magnetic resonance elastography (commonly known as MRE) have been shown to accurately detect advanced fibrosis.[24] ARFI and 2D shear wave elastography imaging can reliably detect cirrhosis, although the data for transient elastography and MRE are more robust.[25,26] However, studies investigating these different modalities that were performed in patients from Asia, Europe and the USA have shown no obvious differences in performance amongst different patient ethnicities.

Epidemiology

Prevalence

The global prevalence of NAFLD varies across different regions. It has been estimated to be around 25.24% of the population based on data from 2016. It is highest in the Middle East followed by South America and Asia. The prevalence of NAFLD in North America and Europe is estimated around 24%, while it was lowest in Africa (Fig. 1).[27] NAFLD is known to occur between the 4th and 6th decades of life,[2] although older age is related to higher rates of developing the disease. Traditionally, it was thought that NAFLD occurred more in men, although some studies dispute this sex bias. The median age of women who develop NAFLD is also higher than that of men.[28] While studies from Thailand and Sri Lanka have found increased prevalence of NAFLD in females, in the USA, China, and Spain the prevalence was higher in men.[29] Many factors, including diagnostic modalities used and inter-country variation in obesity prevalence by sex, could contribute to the sex discrepancies found among studies.

The Dallas Heart Study is a key study that explored NAFLD distribution amongst different ethnicities in the USA.[30] Using magnetic resonance spectroscopy, the investigators observed that there was a significant difference amongst patients of Hispanic, Caucasian, and African American ethnicity with respect to the prevalence of NAFLD, with those of Hispanic origin being more predisposed. Similar data was also derived from the Multiethnic Cohort Study in Hawaii, although the authors reported a significantly increased prevalence in Japanese Americans.[31] Individuals of Alaskan-Native ethnicity have been reported to have a NAFLD prevalence under 5%, although this should be confirmed in future studies.[32]

Studies from both the USA and South America have established that not all patients of Hispanic origin have the same predisposition to NAFLD. While the prevalence among the overall Hispanic population has been reported as high as 29%, within the USA, individuals of Hispanic ethnicity from Mexico had a significantly higher prevalence of NAFLD than patients from Puerto Rico or the Dominican Republic.[33] Moreover, patients from Central America and South America also had higher a prevalence of NAFLD that was not explained by differences in rates of metabolic syndrome, physical activity, or diet.[34] For example, studies from Brazil estimate the prevalence of NAFLD to be around 30%.[35] In a study of patients who underwent bariatric surgery, advanced stage of disease was likely to occur more in Hispanic (43%) and non-Hispanic white (46%) patients compared to non-Hispanic Black (21%) patients.[36]

In Europe, the prevalence of NAFLD varies greatly among the different countries; although similar to patients around the globe, those with metabolic syndrome had a NAFLD prevalence of around 50%.[37] It is worth noting that Eastern

European countries such as Romania reported lower prevalence at around 20% in the same group of individuals.[38] Within European countries, prevalence also has proven to vary among different ethnicities. In Greece, prevalence of NAFLD is reported to be about 41% and in Spain was found to be 33% in males and 20% in woman.[29] In the UK, the highest incidence of abnormal liver tests were among patients of Bangladeshi, Pakistani, and Indian heritage.[39]

Interestingly, although patients of Asian ethnicity have a lower body mass index (BMI) on average than other racial groups, they continue to have a higher prevalence of NAFLD, reported as high as 29.62%, which has increased significantly over the past two decades. The reported prevalence rates from Korea and Taiwan are 24–40% and 15–27% respectively, compared to Japan at 9–18%. Indonesia has the highest prevalence (51.04%).[5]

Although literature from Africa is limited, the reported prevalence was among the lowest worldwide, with Nigeria reporting 8.7% prevalence.[40] In fact, the Dallas Heart Study noted African Americans to have the lowest prevalence of NAFLD in the USA; although, they do have a higher chance of in-hospital mortality, longer hospital stay, and poorer discharge destination compared to non-Hispanic Caucasians.[41] Moreover, a South African study found that progression of fibrosis in patients with NAFLD seems to occur less frequently in those of Black African ethnicity.[42]

A meta-analysis of the literature published on NAFLD from around the world noted that the highest prevalence of NAFLD is in South America and the Middle East.[43] In the Middle East, it is estimated to be 20–30%; although, wide variation appears to exist between various countries. For example, Iran reports the prevalence to be 4.1%, while Saudi Arabia cites 16.6%.[29] Unfortunately, the majority of Middle Eastern countries have not published extensive studies on NAFLD and inconsistencies in regulation, practice, and reporting have affected the quality of data in certain national registries.[44]

Complications/outcomes

Complications and comorbidities of NAFLD are diverse among different ethnicities. The most common cardiovascular complications or comorbidities in China are carotid and coronary artery disease, followed by hypertension.[45] In the USA, African Americans with NAFLD are more likely to have abdominal aorta calcification than non-Hispanic Caucasians, Chinese Americans and Hispanics, with a 41% higher prevalence.[46] In a recent meta-analysis of NAFLD patients comparing patients of different ethnicities, there was no statistically significant difference in severity of fibrosis among Hispanics, non-Hispanic Caucasians, and Blacks. Regarding outcomes of NALFD, including progression to cirrhosis, development of HCC, liver-related mortality and all-cause mortality, the data are heterogeneous.[47] The annual incidence of HCC in Asian countries is higher than the global incidence rate for HCC (1.8 cases per 1,000 person-years *vs.* 0.44 case per 1,000 person-years), which may be related to a lack of public awareness of the disease. Consequently, this may lead to delays in proper intervention, monitoring and screening for HCC in these countries.[29,48]

Some studies suggest that Hispanics have higher rates of disease progression and fibrosis.[30] Data analysis from the Scientific Registry of Transplant Recipients between 2002 and 2019 demonstrated that the rate of NASH is lower in Black patients and the majority of liver transplant waitlist candidates for NASH are of Hispanic ethnicity. Moreover, NASH-HCC is the leading indication for transplantation in Hispanic patients.[49]

Socioeconomic effect

There is a significant socioeconomic effect on NAFLD. Shifting the pattern of lifestyle and diet have contributed to the prevalence of obesity and NAFLD in Asia. The urbanization of countries in Asia promotes the risks of NAFLD in those populations with increasing prevalence of obesity and DM. The lowest prevalence of disease is in Japan, while the highest rates of NAFLD associated-cirrhosis is in Japanese-Americans,[50] suggesting the implication of lifestyle and socioeconomic conditions in the prevalence of NAFLD.[48] Similarly, differences in prevalence of NAFLD between Africans in Nigeria and African Americans indicates the implication socioeconomic effect on the epidimology.[51] The prevalence among the younger Chinese population (<60 years-old) was also higher compared to similarly aged patients in the West that is due to rapidly increasing in prevalence of NAFLD from 2008–2010 to 2015–2018 along with rapid change in socioeconomic status.[45] A population-based study in southwest Iran suggested that patients with a high socioeconomic level were likely to have NAFLD.[52] On the other hand, socioeconomic conditions impact the outcomes of NAFLD. The proportion of deaths from NASH was lowest in the high-income Asia Pacific region.[51] Poor awareness of NAFLD and less health care utilization in China may contribute to the higher incidence of HCC.[45,53,54]

Risk factors

Weight

The World Health Organization estimated in 2016 that there are more than 1.9 billion adults who are considered overweight or obese.[29] The USA has the highest overall number of obese adults and Indonesia is reported to have the lowest. In terms of prevalence, Oceania has the highest prevalence, while the Middle East is second in prevalence.[29] A recent study demonstrated lower rates of overweight and obese individuals in China, with a higher prevalence and incidence of NAFLD than Western countries. Genetic factors with an involvement in high frequency of NAFLD promotion genes and low frequency of NAFLD risk reduction genes might contribute to the predisposition of NAFLD and metabolic disease in the Chinese population.[45,48] The World Health Organization has classified Asians with BMIs of 23–27.5 kg/m^2 to be at increased risk of obesity-related conditions.[55]

NAFLD in lean individuals, which is commonly defined as NAFLD in patients with a BMI <25 kg/m^2, has been studied among different ethnicities and nationalities, including Asians, Indians, and Caucasians. The overall prevalence of lean NAFLD is 5–26% in Asian populations, and 7–20% in Western populations. These data should be interpreted with caution, given the different BMI cut-offs among different regions. Among Asian countries, the prevalence ranges from approximately 7.27–8% in China, 4.2% in Taiwan, 19.3% in Hong Kong, 12.6–22.4% in Korea, 15.2% in Japan, and 6.4% in India. Compared to Asia, the data in Caucasians are sparse, with smaller sample sizes. A meta-analysis of 93 international studies estimates that 40% of patients with NAFLD globally are non-obese and an estimated 20% were classified as lean NAFLD. The prevalence of non-obese NAFLD notably varied quite significantly amongst different countries, with a reported prevalence as low as 25% in Pakistan to more than half of the general Austrian and Swedish population.[56] Other country specific studies have reported lean NAFLD rates of 16% in Italy, 17% in the Dallas Heart Study, and 7.4% in the largest epidemiological study in USA. Lean NAFLD is associated with proinflammatory

visceral adipose tissue, central obesity, higher triglyceride level and early adulthood weight gain in Asian populations, whereas it is associated with insulin resistance, younger age, female sex, and hypercholesterolemia in the Caucasian population.[57] Another study demonstrated 2- to 3-fold higher risk of insulin resistance in Asian Indians compared to matched Caucasians, Africans, and Eastern Asians.[58] A multiethnic study in the USA also showed that non-obese Hispanics, Chinese Americans, and South Asians were at higher risk of being metabolically ill health compared to non-Hispanic Caucasians due to insulin resistance.[59]

In longitudinal studies, development of advanced liver disease in lean NAFLD is associated with hypertriglyceridemia and higher creatinine in Asians. Moreover, lean NAFLD patients in one study were more likely have disease progression compared to obese NAFLD patients amongst Caucasians.[57] In fact, global estimates of NASH and stage 2 or greater fibrosis in non-obese and lean NAFLD patients are 39.0% and 29.2%, respectively. Consequently, this has been linked to all-cause, liver-related, and cardiovascular-related mortality rates of 12.1, 4.1, and 4.0 per 1,000 person-years in this particular demographic.[56] A multicenter study from Italy further classified the risk of disease progression and comorbidities in lean *vs.* obese patients with NAFLD. In this patient cohort, individuals with lean NAFLD were less likely to have metabolic syndrome and its associated complications, including hypertension, diabetes and carotid artery disease, and less likely to have NASH or advanced fibrosis compared to overweight and obese NAFLD patients. Interestingly, waist circumference appeared to be an important factor in determining the risk of associated comorbidities and disease progression. In fact, lean NAFLD patients with a medium waist circumference (men: 94–102 cm; women: 80–88 cm) were more likely to be diabetic than overweight and obese patients with a similar waist circumference. In the overall study population, individuals in the highest waist circumference category were at the highest risk for disease progression, regardless of BMI.[60] Factors that might contribute to lean NAFLD encompasses concomitant alcohol intake, endocrine disorders (polycystic ovarian syndrome, hypothyroidism, growth hormone deficiency), congenital and acquired lipodsystrophy from human immunodeficiency virus medications, association with certain drugs (such as steroids, amiodarone, methotrexate and tamoxifen), inborn errors of metabolism (lysosomal acid lipase deficiency), genetic factors [polymorphisms in the gene that encodes for patatin-like phospholipase domain-containing protein 3 (*PNPLA3*)], nutritional factors (starvation, total parental nutrition), and gastrointestinal surgery (jejunoileal bypass).[61]

Metabolic syndrome

Metabolic syndrome (MS) includes abdominal obesity, DM, hypertension, and dyslipidemia.[62] Both obesity and DM are increasing globally and are correlated with increased prevalence of NAFLD. Type 2 DM is a major risk factor for the development of NAFLD and accelerates progression to advanced liver disease and increase risk for mortality. According to the World Health Organization, there has been an increase in DM from 108 million in 1980 to 422 million in 2014, with a notable increase amongst patients in low and middle income countries.[63] The prevalence of NAFLD/NASH among type 2 DM is over 60%.[64] Similarly, the prevalence is 52.55% in Asians.[48] In the USA, Hispanics have a 12.8%, non-Hispanic Blacks have 13.2% and Asian Americans have 9% higher risk of type 2 DM, respectively, when compared to non-Hispanic Caucasians.[65] Native American adults in Southern Arizona have one of the highest prevalence rates of DM in the world, estimated at 33%. According to the 2019 International Diabetes Atlas, the prevalence of diabetes in adults was 8.5% in South and Central America, 12.2% in the Middle East and North Africa, 4.7% in Africa, 11.5% in South-East Asia, 11.4% in the Western Pacific, and 6.3% in Europe.[65]

Hypertension is another risk factor for NAFLD and has a bidirectional relationship with NAFLD. The severity and progression of NAFLD have been associated with hypertension. On the other hand, NAFLD is also a possible risk factor for development of hypertension.[66] In the USA, the prevalence of hypertension is higher in non-Hispanic Blacks compared to non-Hispanic White and Hispanic populations.[67] When the 2017 American College of Cardiology/ American Heart Association hypertension guideline was applied globally, the prevalence of hypertension increased in Canada (32% to 46%),[68] India (29% to 43%),[69] China (25% to 50%),[70] and South Korea (28% to 48%),[71] respectively.

Dyslipidemia induces inflammation and increases cytokine production and oxidative stress, triggering pathogenesis of NAFLD. Moreover, dyslipidemia is responsible for cardiovascular risk in NAFLD patients.[72] Hypertriglyceridemia was found to be highest in East Asians and non-Hispanic Whites and lowest in the African American population.[73] The prevalence of high low-density lipoprotein cholesterol was higher in Asian Indians, Filipinos, Japanese, and Vietnamese compared to non-Hispanic Whites.[74] MS was found to be present in 34%, 62%, 31%, 33%, and 37% of patients with NAFLD in Asia, Europe, Middle East, North America and South America, respectively. The incidence of MS is higher among NAFLD patients compared to controls. In Asia, the incidence increases by 14% if patients have at least three components of MS compared to patients with fewer MS.[5] NAFLD patients with multiple components of MS are at higher risk for advanced fibrosis and all-cause mortality. Each additional MS condition worsens the risk of liver-related and all-cause mortality based on The Third National Health and Nutrition Examination Survey (commonly known as NHANES).[75]

Genetics

With the advent of genome-wide association studies (commonly referred to as GWAS), many genes have been brought to the forefront of NAFLD research. A select few of these genes have been further explored with respect to their role in NAFLD development in different ethnicities, and many more are under investigation.

One of the most notable genes in the field of NAFLD codes for PNPLA3. In particular, the genetic variant rs738409, which results in substitution of methionine for isoleucine, resulting in a loss of function in the PNPLA3 protein, contributes to increased accumulation of triglycerides in lipid droplets within hepatocytes as compared to cells with functional PNPLA3.[76] This variant has been associated with increased susceptibility to NAFLD in a variety of different ethnicities, including Hispanics, African Americans, East Asians, and South Asians. Particularly in studies from Asia, a "lean NAFLD" phenotype, as previously mentioned, is well described. These patients have a BMI that is lower than the commonly accepted obese range, and yet still develop NAFLD at notable rates.[77] A study from Hong Kong noted that the rs738409 allele is more common in patients with "lean NAFLD" than in obese patients.[78] Another gene variant of *PNPLA3*, rs6006460, results in a phenotype characterized by lower than average hepatic fat. This variant, interestingly, occurs in 10% of African Americans as opposed to <1% in either Caucasians or Hispanics,[79] and may in part explain the lower observed incidence of NAFLD amongst this

patient demographic.

Another gene linked to the development of NAFLD that has also been studied within the context of ethnicity codes for the membrane-bound o-acyltransferase domain-containing 7 protein. The rs641738 variant has been associated with increased NAFLD risk in Europeans[80] but has not been studied in other populations as extensively. Two other genes with variants associated with NAFLD, *TM6SF2* and *GCKR*, have been well described. *TM6SF2* codes for a protein of unknown function, although different variants have been linked to increased hepatic lipid content, as well as increased levels of aspartate aminotransferase/alanine aminotranferase.[81] *GCKR*, which codes for a glucokinase regulator, similarly has variants that are associated with hepatic fat accumulation.[82] A population-based study among Hispanic/Latino adults in the USA found a high frequency of *PNPLA3* G (41%) and a low frequency of *TM6SF2* T (5%) in Hispanics/Latinos. Among Hispanics, the *PNPLA3* G frequency was the highest in Mexicans (52%) and the lowest in Dominicans (23%).[83] In another study that compared genetic predisposition between Chinese and Caucasians, the frequency of *PNPLA3* polymorphism was higher and that of *TM6SF2* was lower in Chinese compared to Caucasians.[45]

GWAS studies have also yielded a number of different genes associated with NAFLD, including but not limited to *LPIN1*, *Tribble-1*, *FDFT1*, *ERLIN1, etc.* Genes involved in the pathophysiology of other liver conditions have also been noted to contribute to risk of NAFLD development; for example, mutations in *HFE*, most commonly noted in hereditary hemochromatosis, have been cited as risk factors for NAFLD.[84] It is also worth mentioning that ongoing investigations into epigenetics, microRNA, and mitochondrial RNA may improve our understanding of how NAFLD presents in different ethnicities in the future.

Lifestyle

Diet

Although it seems intuitive that certain elements of diet and weight control would predispose specific populations to NAFLD, the literature that explores these factors is more recent. Overall, increased intake of saturated fats, fructose, and cholesterol-rich sources predisposes individuals to NAFLD.[85] Although evidence currently is limited, sedentary behavior has been increasingly accepted as an independent risk factor for NAFLD.[86] As an example to the beneficial effect of physical activity, aerobic exercise that contributes to progressive increase in fat-free, lean mass can provide protection against NAFLD. Dietary elements typical of the Western Diet in addition to Western eating habits, such as snacking, have been shown to independently contribute to hepatic steatosis.[87] Soft-drink consumption, rampant in the West, has been shown to increase liver fat by 140% over a period of 6 months in otherwise healthy individuals.[88] Relatedly, it was found that a diet of 3 g fructose/kg increases the amount of hepatic fat in adult men.[89]

Limiting consumption of carbohydrates has generally been noted to improve NAFLD;[90] however, if carbohydrates are examined overall, a focus on ethnic diet variations presents a more complicated picture. For example, the traditional Chinese diet is high in carbohydrates but is also vegetable-rich and has proven to be low-risk for NAFLD. Consistent with earlier mentioned data, a more recent study noted that "Westernization" of South Korean food, via refined grains, processed meats, fried foods, *etc.*, correlated with increased incidence of NAFLD diagnosed by ultrasound.[91] Such regions have also noted that weight gain in general, irrespective of diet, seems to predispose people to NAFLD in certain regional studies. Korean studies have noted that weight gain as low as 2 kg can contribute to NAFLD development.[92] More specifically, data from Hong Kong reported that the presence of central obesity predisposes patients to NAFLD.[93]

Variations and similarities in the standard diet within a geographic region or amongst individuals of a particular ethnic background has allowed researchers to investigate the different nutritional patterns that promote hepatic steatosis and the progression of NAFLD, as well as whether a specific diet affects disease progression differently in patients of various backgrounds. Ultimately, this informs healthcare providers when counseling patients with NAFLD on ideal eating habits, and whether recommendations can be generalizable to individuals of various ethnicities.

The Western dietary pattern, containing large amounts of red meat, processed meat, and fried foods, has a well-established link to the development of MS.[94] Unfortunately, this diet has established itself and its associated adverse health consequences globally. A study of 170 Iranians with NAFLD evaluated the effects of an Iranian, Western and "healthy dietary patterns" on liver fibrosis. The Western dietary pattern was strongly associated with fibrosis, with an odds ratio of 4.21. The investigators noted that higher consumption of red meat, hydrogenated fats, and soda drinks increased the odds of fibrosis measured by elastography, while a diet rich in low-fat diary, nuts, fruit, and coffee or tea was protective.[95] Interestingly, the positive association between a Western diet and NAFLD was not replicated in a prospective cross-sectional study of 1,190 Korean patients with and without NAFLD. Four dietary patterns and their association with a diagnosis of hepatic steatosis were analyzed, including a traditional Korean diet, Western and high-carbohydrate diets, and a simple meal pattern diet. As previously mentioned, this study revealed no association between a Western or carbohydrate-rich diet and the presence of NAFLD, while a traditional Korean diet was positively correlated with presence of the disease.[96] While the absence of an association between increased carbohydrate intake and NAFLD is somewhat surprising, data from other studies have been inconsistent with regards to the effect of carbohydrate intake. Patients who were on a 2-week carbohydrate-restricted diet had similar weight loss but more hepatic fat reduction than patients who were on a reduced calorie-only diet.[90] However, another study demonstrated similar improvements in hepatic steatosis between patients on a high-carbohydrate diet and low-carbohydrate diet when weight loss was comparable,[97] suggesting that the true benefit of carbohydrate restriction on NAFLD arises primarily when it is linked to weight reduction. However, a low carbohydrate diet in patients with NAFLD has been associated with a decrease in alanine aminotransferase, although the diet was primarily soy-based.[98]

In contrast to the Korean dietary study and similar to findings of the Iranian investigators, a study out of Greece confirmed the increased odds of NAFLD with a fast-food type dietary pattern, while also confirming that when unsaturated fatty acid intake was divide into quartiles, those in the second quartile had an over 50% reduced odds of NAFLD compared to individuals within the first quartile of dietary intake.[99] With respect to fats, a potential therapeutic strategy includes increased consumption of both mono-unsaturated fatty acids and poly-unsaturated fatty acids. Increased intake of poly-unsaturated fatty acids results in greater reduction in hepatic steatosis when used in combination with a heart healthy diet compared to dieting alone.[100] In fact, a meta-analysis has found that omega-3 fatty acids derived from seafood sources have a positive effect on hepatic steatosis.[101]

Given the increased popularity and presence globally of the Western style diet, the above data generally seem to

suggest a benefit to avoiding this type of nutritional behavior. In fact, a study assessing patients (Framingham Heart Study), consisting primarily of Caucasian patients in the USA reinforced the benefits of focusing on alternative diets for liver fat accumulation. The study investigated how changes in the Mediterranean-style diet score and Alternative Healthy Eating Index affected liver fat and new-onset fatty liver. An increase in either dietary score was inversely associated with liver fat accumulation and incident NAFLD, with a reduction in the odds of fatty liver by 26% for every 1-standard deviation increase in Mediterranean-style diet score. Moreover, individuals with a higher genetic predisposition to NAFLD as determined by single nucleotide polymorphisms and decreased Mediterranean-style diet score or Alternative Healthy Eating Index scores had higher liver fat compared to patients with improved or stable scores.[102] Thus, adopting the Mediterranean diet, typically characterized by high intake of olive oil, nuts, fruits, vegetables, legumes, and fish, with wine in moderation, can be suggested to patients with NAFLD, especially given the broad health benefits related to a variety of different health conditions related to MS. Despite heterogeneity in the way the Mediterranean Diet is defined in different studies, it has consistently shown favorable health outcomes.[103] Studies from multiple regions of the world have reported a marked regression of NAFLD when patients switched to the Mediterranean Diet,[104] reinforcing its broad appeal regardless of patient ethnicity. A large randomized control trial to evaluate the benefit of this diet, independent of weight loss, is currently underway in Australia.[105]

With respect to protein intake, it seems that a diet consisting of a larger proportion of protein does not necessarily aid in improvement of NAFLD. However, a moderate protein diet encompassing 25% of total caloric intake has been shown to be optimal, and higher percentages do not necessarily reduce body fat content any better.[106]

Ultimately, the guidance provided by a patient's healthcare provider is key to successful changes in dietary habits that can ultimately improve or reverse hepatic steatosis. Studies show that patients will make better nutritional choices after having expressed better understanding of what NAFLD is, reinforcing the importance of patient education. Moreover, as a preventative measure, recommending dietary patterns that reflect an adherence to a healthy diet can reduce NAFLD risk in the general population. An analysis of the multiethnic cohort consisting of patients of African American, Japanese American, Latino, Native Hawaiian, and Caucasian descent revealed that high Healthy Eating Index and Dietary Approaches to Stop Hypertension scores were associated with lower risk of fatty liver, with no observed differences by race or ethnicity.[107] However, a more recent analysis of the same cohort focused on the specific components of enrollees' diets at baseline and association with NAFLD. Overall, when comparing 2,974 patients with NAFLD and 29,474 matched controls, intake of poultry, cholesterol, processed red meat and red meat in general was associated with NAFLD. When stratified by race and ethnicity, poultry intake and cholesterol intake was only significantly associated with NAFLD in Whites and Native Hawaiians. Processed red meat correlated significantly with NAFLD in Latinos and Whites, and increased fiber intake was protective in these two ethnic groups.[108] The damaging effects of red meat consumption and the associated risk of NAFLD was further demonstrated in a cross-sectional study of 789 adults. After controlling for BMI, smoking, alcohol intake, physical activity, energy and saturated fat and cholesterol intake, the consumption of meat in general and red or processed meat was associated with increased odds for insulin resistance and NAFLD.[109] Thus, while an overall healthy diet is recommended for all patients, with the ultimate goal of achieving meaningful weight loss, a specific list of foods to avoid may be tailored to a patient based on race and ethnicity.

Intermittent fasting has recently gained popularity as an alternative to more traditional diets, aimed at reducing weight and improving obesity-related comorbidities. It includes diets that focus on a particular eating pattern where caloric intake is eliminated during a predefined period of time, and has consistently proven beneficial for both weight loss and reduction in obesity-related comorbidities.[110] A randomized controlled trial assessing a modified alternative-day calorie restriction diet, another form of intermittent fasting, found that adherence to this diet amongst patients with NAFLD was excellent (75–83%) with a significant reduction in liver steatosis and fibrosis (measured by shear wave elastography) amongst individuals randomized to 8 weeks of the intervention diet arm.[111]

Physical activity

Exercise as an intervention in NAFLD has also been studied, although the data concerning its benefits independent of the weight loss requires further clarification. Studies have noted a 20–30% decrease in hepatic lipid content with general exercise. Interestingly, even when these patients regain lost weight, there seems to be a persistent long lasting beneficial effect on liver fat and insulin resistance.[112] Aerobic exercise has been shown to reduce hepatic triglycerides in sedentary and obese patients.[113] Weight resistance exercise has also been linked to a reduction in hepatic steatosis without weight loss.[114] Although evidence on aerobic *vs.* resistance training is mixed, combination therapy seems to be superior to either. However, weight loss was a confounder when comparing aerobic with resistance exercise and a combination of the two,[115] and thus these recommendations require further investigation prior to unlinking their benefits to weight loss alone.

Non-obese patients with underlying NAFLD or NASH can be more challenging to manage in the absence of approved pharmacotherapy. As mentioned previously, the strongest evidence for the management of NAFLD and NASH comes from studies focused on interventions that achieve weight loss and increased physical activity. While implementing these interventions intuitively makes sense in obese individuals or those with other components of MS, it is less obvious for those considered within normal BMI range, which has been more commonly seen in patients of east Asian background.[116] However, a study examining the effect of diet modification and exercise on hepatic steatosis in 1,365 potential living donors with NAFLD on initial biopsy revealed that although only 5% of patients were obese at the start of the study, histological improvement on repeat biopsy was observed in 85.8% of participants.[117] Some of these findings may, in part, be related to the response to weight loss seen with variants of the *PNPLA3* alleles. More specifically, the GG genotype that is more commonly observed in Asian patients with "lean NAFLD" has been linked to a favorable histologic response to diet modification leading to weight loss. Thus, despite the challenges associated with recommending weight loss to patients with a normal BMI, interventions that reduce weight are likely to be beneficial in this patient population. Moreover, although "lean NAFLD" is well recognized in patients of Asian background, with prevalence as high as 19% in Asia compared to 7% in the USA, this phenotype is now increasingly recognized in other races. In fact, a large Swedish cohort with 646 patients with biopsy-proven NAFLD, the "lean NAFLD" prevalence was reported as 19%,[118] identical to estimates from Asia, making these recommendations more generalizable than previously thought.

Studies assessing the efficacy of caffeinated beverages

have shown consistent results. Overall, while the majority of studies do not show any significant improvement in steatosis with increased caffeine intake, coffee and other caffeinated beverages may have a protective effect against the development or presence of fibrosis.[119] An analysis of the multiethnic cohort evaluating the association between coffee intake and chronic liver disease and HCC revealed an inverse association between increased coffee consumption and the incidence of HCC or chronic liver disease. In fact, consuming ≥4 cups of coffee a day was associated with a 41% reduction in HCC and a 71% reduction in chronic liver disease, when compared to non-coffee drinkers. This association did not differ based on patient race or ethnicity. Given the risk of HCC associated with NAFLD, including in the absence of cirrhosis, a balanced increase in coffee intake may be beneficial regardless of race.[120]

Conclusions

The prevalence of NAFLD varies globally. Different ethnicities carry distinct risks for NAFLD. The shifting paradigm of socioeconomic status, lifestyle, and dietary habits plays an important role in raising the incidence of NAFLD irrespective of genetic and geographic background. Those changes are diverse among different ethnicities and/or countries. The disparity in availability and accessibility to certain diagnostic tests and healthcare utilization in different countries also impacts the rates of outcomes or complications. We have briefly summarized the characteristics of NAFLD in different ethnic populations in Table 1. While it is important to develop universal guidelines that can be used for patients of any ethnic background, it is also imperative that diagnosis and management of NAFLD is tailored differently amongst various populations. We need more effort in educating patients on NAFLD and improvement in the utilization of non-invasive tests to risk-stratify these patients. Obtainment of more data on socioeconomic effects of NAFLD is necessary, as such plays a major role in development and complications of NAFLD. Finally, it is important for nations to work together to implement education and prevention programs to decrease the growing burden from this disease.

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Conflict of interest

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Author contributions

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Table 1. Summary characteristics of NAFLD in different ethnicities

Ethnicity	Characteristic
Caucasian	More obese NAFLD than lean NAFLD
Hispanic	Leading cause of NASH-HCC transplant in the USA
Asian	More lean NAFLD than other ethnicities Urbanization and change in pattern of lifestyle and diet contributed to NAFLD Poor awareness of NAFLD and less health care utilization
Non-Hispanic Black or African American	Higher chance of in-hospital mortality, longer hospital stay and poorer discharge destination Need more data on prevalence in Africa

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