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Global Epidemiology of Non-Alcoholic Fatty Liver Disease and Perspectives on US Minority Populations

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Abstract

Non-alcoholic fatty liver disease (NAFLD), a clinical syndrome that is predicted to affect millions of people worldwide, will become the next global epidemic. The natural course of this disease, including its subtype, non-alcoholic steatohepatitis (NASH), is not clearly defined, especially in the US minority populations. The aim of this review is to report the global epidemiology of NAFLD, with emphasis on US minority populations on the basis of database searches using Pubmed and other online databases. The US Hispanic population is the most disproportionately affected ethnic group with hepatic steatosis whereas African-Americans are the least affected. Genetic disparities involved in lipid metabolism seem to be the leading explanation for the lowest incidence and prevalence of both NAFLD and NASH in African-Americans.

Keywords

Epidemiology; obesity; African-Americans (AAs); non-alcoholic fatty liver disease (NAFLD); non-alcoholic steatohepatitis (NASH); insulin resistance (IR); metabolic syndrome (MetS)

Introduction

NAFLD is a disorder of hepatic lipid storage that manifests as either simple steatosis or as NASH, the latter which is characterized as hepatic fat accumulation accompanied by

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inflammation which over several years can progress to more advanced liver disease. NAFLD, which develops in the presence of relatively low alcohol consumption, typically < 14 units per week, [1, 2] is now considered as the hepatic manifestation of the metabolic syndrome (MetS). The diagnosis of the MetS requires the presence of three of five factors: hypertriglyceridemia, low concentrations of high-density lipoprotein-cholesterol (HDL-C), central obesity, hypertension, and fasting hyperglycemia [3].

Population-based cohort studies have reported that mortality in NAFLD is increased over a period of 10 years when compared with a healthy control population [4], attributed primarily to cardiovascular and liver-related mortality in addition to malignancy. Biochemical and clinical features suggestive of more advanced liver disease are used to calculate the NAFLD fibrosis score and the FIB-4 index, simple and easy identifiers of patients at high risk for advanced liver disease [5, 6, 7].

The disease burden of NAFLD mirrors the rapid recent rise in the incidence of diabetes, obesity and the MetS [4]. The real burden of NAFLD most likely remains underestimated due to i) the long natural history of fibrosis development in NAFLD; ii) a mortality that often is not liver-related and iii) the lack of disease awareness in the physician as well as patient communities [8, 9]. Furthermore, since NAFLD can also coexist with other liver diseases such as chronic hepatitis C, differentiation of HCV from NAFLD as the primary driver of disease progression may be difficult.

This review will provide global perspectives on the prevalence of NAFLD with special emphasis on the epidemiology of the disease in US minority populations.

Diagnosis of NAFLD in epidemiological studies

The American Association for the Study of Liver Diseases (AASLD) defines NAFLD as hepatic fat accumulation in the absence of alcohol consumption that exceeds 140 g/week for men and 70 g/week for women in the last 12 months, respectively in the absence of chronic liver diseases associated with fat accumulation as well as certain drugs and systemic diseases [2]. The degree of steatosis and the absence or presence of inflammation and fibrosis are primarily determined by liver biopsy.

Since for practical reasons most epidemiologic studies base NAFLD characterization on surrogate disease markers and not on biopsy results, interpretation of their data may be limited. Although not highly specific or sensitive, these surrogate markers include elevated liver-associated enzymes such as aspartate aminotransferase (AST) and alanine aminotransferase (ALT) [10, 11] as well as imaging tests such as abdominal ultrasound [US], computed tomography [CT]), or magnetic resonance imaging (MRI). The imaging tools may not provide consistent data due to varying interpretations of the data by radiologists [12]. Although liver biopsy is the standard benchmark for the most accurate diagnosis of NAFLD and NASH, it can still beset with sampling and interpretational errors, since, for example, simple steatosis may be less evident or even absent once the disease has progressed. The best alternative noninvasive quantitative measuring tool is proton magnetic resonance spectroscopy, which defines NAFLD as hepatic fat accumulation (steatosis) > 5%

of total weight of the liver. Unfortunately this tool is not widely available and hence ultrasonography is most commonly used to identify those with fatty liver.

The vast majority of epidemiologic studies have documented the prevalence of individual diseases in selected tertiary hospital populations [13]. This common practice, particularly when imaging and liver enzyme tests are involved and when patients may be asymptomatic in the early disease stages, underestimates the presence of NASH while overestimating the prevalence of NAFLD, in particular for minority populations in whom the natural development and progression of NAFLD and NASH are understudied and underreported, as reflected by the paucity of available published data.

Since the fundamental principles underlying the control and prevention of diseases are largely based on data obtained from epidemiologic studies, accurate disease diagnosis is of considerable importance. To improve diagnostic accuracy, there is an urgent need for the development of a less-invasive method than biopsy and for a more sensitive biomarker than alanine transaminase (ALT) for large-scale NAFLD screening. The lack of high-throughput studies involving proteomics or metabolomics for the discovery of novel and reliable diagnostic biomarkers for NAFLD also hampers epidemiologic studies.

Epidemiology

The prevalence of NAFLD, which is highest in populations with MetS and pre-existing metabolic conditions including obesity and type II diabetes (T2DM), is due to the presence of a close connection between NAFLD and the twin components of diabetes, MetS and insulin resistance (IR), sometimes also referred to as cardiovascular risk factors. A preponderance of the studies investigating the natural history of NAFLD validate the progression of NAFLD to NASH, often proceeding to advanced fibrosis and hepatocellular carcinoma (HCC) [14-16]. Recent data confirm that NAFLD and NASH correlate equally to obesity and type 2 diabetes globally (e.g. in Africa, Asia, Australia, Europe, the Middle East, North America, and Latin America; see Table 1 for references). Epidemiologic studies lend credence to the unidirectional relationship between NAFLD and the MetS, the latter which may be the etiologic agent that triggers the pathophysiological cascade of NAFLD. Yet, the literature also suggests that the relationship between NAFLD and MetS may be bidirectional. Nonetheless, the prevalence of NAFLD varies according to age, sex, and the methodology used to measure the condition in each geographical location. The prevalence rates documented in this review mostly reflect data collected from urban centers whose NAFLD incidences may not necessarily mirror those from rural areas in developing countries. In this review, the prevalence is specified according to the type of epidemiologic study. Therefore, the estimates may also vary depending on the source of the study and whether it is population- or single center-based study. Moreover, most of the reviewed literature with respect to population-based studies defines NAFLD as hepatic steatosis without secondary causes and diagnosed with ultrasound in the absence of other known liver diseases.

Global Perspectives

According to the World Gastroenterology Organization's global guidelines (<http://www.worldgastroenterology.org/UserFiles/file/guidelines/nafl-d-nash-english-2012.pdf>) and population-based studies emanating from different countries, NAFLD is becoming the most common cause of liver disease in the world. Some of the confounding factors that may contribute to this rise in NAFLD incidence include alterations in dietary habits and the increased prevalence of MetS components such as central obesity and diabetes type 2 (T2DM) [17]. Furthermore, NAFLD was only recently defined and characterized [15] in contrast to alcoholic fatty liver disease (AFLD); and therefore, one of the reasons for its apparent rising incidence could also be the result of increasing awareness by caregivers and healthcare providers since the initial description of NAFLD was published by Ludwig et al. in 1980 [18]. The prevalence of NAFLD (4-46%) varies across the world based on demographics, the diagnostic methodologies used, and by disease epidemiology [13, 17]. The prevalence of NAFLD and to a lesser extent, NASH, in adults and children, in many parts of the world is shown in Table 1. Those studies using elevated liver enzymes to indicate the ostensible prevalence of NAFLD have reported prevalence ranging from a lower limit of 2.6-5.4% in the United States [19] to 9.3% in Japan [20]. When imaging is used as the diagnostic tool, the prevalence estimate implicating it as the primary cause of chronic liver disease is higher (19 - 45%) [18, 21, 22]. In the Western hemisphere (where the prevalence is between 2-40%), contemporary lifestyles and dietary habits have been cited as contributors to obesity and IR [23, 24]. Similar lifestyle alterations have been reported for the current prevalence of NAFLD in Africa, Asia, Australia, the Middle East, and Latin America (Table 1).

For decades, viral hepatitis-induced liver disease and alcohol-triggered liver disease were the primary causes of liver injury and liver failure in the United States and other parts of the world. Nonetheless, the improving control of hepatitis B and hepatitis C and the concomitant global rise in the prevalence of obesity have enabled NAFLD to emerge as a major global health threat and the second-leading indication for liver transplantation [25]. It is predicted that along with an aging population and contemporary lifestyle behaviors, the burden of NAFLD, including cirrhosis, hepatocellular carcinoma, and the need for liver transplantation will increase even more substantively over the next twenty years. The estimates of NAFLD prevalence across populations do not conform to a standard definition or diagnosis of the disease due to variations in diagnostic methodologies across the world. But, as a rule, the prevalence of NAFLD increases with age and is higher in males [26, 27]. In the case of African-Americans as well as in Hispanics, additional risk factors are type 2 diabetes and genetic factors [28]. A good barometer to gauge the true penetration of NAFLD in the general population was reported when apparently healthy (non-obese) and relatively young living liver donors with little or no alcohol consumption were reported to have prevalence of NAFLD from 17.9% in Japan [29] to 34% in the United States [30]. Conversely, the global prevalence of NASH is 3 - 5% [13].

US Perspectives

The US National Health and Nutrition Examination Survey (NHANES), which conducts interviews and physical examinations for population studies, reports that the percentage of NAFLD among chronic liver diseases in the US increased from 47% in 1988 to 75% in 2008 [18], which may be attributable to a rise in the prevalence of obesity, IR, and alterations in dietary habits. In the United States, the progressive form of NAFLD, NASH, is now the number two indication for liver transplantation [31]. Table 2 depicts NHANES data on the prevalence of nonalcoholic fatty liver disease in population-based studies.

Among all ethnic groups in the USA, Hispanics are the most exposed to NAFLD, with obesity, the cardinal component of MetS, a significant contributor to fatty liver disease and other obesity-related illnesses [32-36]. US Hispanics are not a monolithic block but rather a diverse group of individuals from varying cultural backgrounds and diverse genetic ancestry [37]. Although the majority are Mexican-Americans, cautionary interpretation should be considered about the generalization of the prevalence of NAFLD or NASH in the Hispanic population of the United States [35]. Obese individuals have a higher prevalence of NAFLD than non-obese individuals [38, 39]. Obese adolescents with MetS have a 5x higher risk of NAFLD than those without MetS [40]. Estimates are that 66% of the United States population is overweight as measured by body mass index (BMI) ($> 25 \text{ kg/m}^2$) and about 32% is obese with BMI ($\geq 30 \text{ kg/m}^2$) [33]. Also, $> 80\%$ of obese subjects in the US are affected by NAFLD in contrast to $\sim 30\%$ in the general population [34]. Furthermore, the prevalence of NAFLD in the adult US population is 20 - 40% [13, 18] and 10 - 20% in children [41]. In a community-based Framingham Heart population study in which the overall prevalence of NAFLD was 17%, the prevalence in men was 19%, in women 15%, and 90% in patients expressing interest in bariatric surgery [26, 27]. In contrast, the prevalence of NASH, which is a major contributor to fatal cardiovascular diseases, is 3 - 5%. Also, 25 - 30% of NAFLD patients eventually progress to NASH, [18, 42, 43]. Although the factors underlying the progression of NAFLD to NASH are not fully understood, it is known that most of the NAFLD-diagnosed individuals do not develop NASH [44]. Nonetheless, NASH with fibrosis occurs in $\sim 40\%$ of patients harboring MetS [45]. Among obese individuals and particularly patients with hyperlipidemia, the prevalence of NAFLD is 60 - 85% [15], whereas in diabetic patients, the prevalence is 30-50% [46], and in obese children it spikes to 40-70% [47]. Moreover, the prevalence of pediatric NAFLD increased from about 3% a decade ago to 5% today, with a male/female ratio of 2/1. Thirteen percent of patients with NAFLD and especially NASH experience increased mortality risk due to liver disease, 25% due to cardiovascular disease, and 28% due to liver cancer such as hepatocellular carcinoma (HCC) [4]. In the absence of cirrhosis, the main risk factors for HCC are NAFLD and MetS [48]

A 10-year follow-up of Mayo Clinic liver disease-related mortality data obtained from US NAFLD subjects reported that malignancy (28%) was the most common cause of death followed by ischemic heart disease (25%) and liver disease (13%). Yet, later biopsy and autopsy studies from the same report revealed that the ultimate cause of death was NASH [4]. For high-risk patients, prior to surgery, liver disease is often unsuspected until the intraoperative liver biopsy reveals NAFLD. In such a case, simple steatosis is observed in

30-90% of the patients, and steatohepatitis in 33 - 42% of the cases [49]. Moreover, idiopathic portal fibrosis (33%) and advanced fibrosis (12%) are observed in morbidly obese gastric bypass patients. A study conducted in a diabetic clinic in a tertiary center revealed that the prevalence NAFLD is higher in type 2 diabetic patients than non-diabetic patients [50]. Ultrasonography, which is relatively insensitive for the diagnosis of fatty liver, detected that 50% of these diabetic patients had fatty liver. Liver biopsy confirmed that 12% of these had NAFLD (simple steatosis) and extensive fibrosis (i.e. cirrhosis) was present in 20% of these diabetics. Since nearly half of the patients with NASH die of cardiovascular disease and malignancy [51, 52], NASH may thus be overlooked or underdiagnosed at the initial stage of diagnosis. As biopsy may not be a practical diagnostic test for all suspected fatty liver diseases, alternative noninvasive tests that are cheaper and easier predictors of NAFLD in large populations are needed. A good example is the Dionysus 'fatty liver index' (FLI), which is a continuous score based on four variables: BMI, waist circumference, serum triglycerides, and γ -glutamyl transferase. A recently published report indicates the development of a new noninvasive marker for early diagnosis of NASH and NASH-related fibrosis using serum biomolecules identified through pathway analyses [53]. This technique, if vigorously validated, may become a useful alternative diagnostic tool to liver biopsy and ultrasonography.

Hepatic sonography of 95 adult clinic patients with dyslipidemia (high triglyceride and low-density lipoprotein [LDL] elevations) detected fatty liver in 50% of the patients [52]. The risk factors for cirrhosis in these patients include older age (i.e. >45-50 years), obesity and type 2 diabetes. These factors comprise 66% of the prevalence of bridging fibrosis. Comparison of patients with NAFLD to other liver disease patients reveals that there is a 15% prevalence of extensive fibrosis (i.e. F3-F4) in NAFLD patients considering gastric bypass surgery and 25% prevalence in older NAFLD diabetic patients. This fibrosis level is similar to alcohol abusers and hepatitis C (HCV) patients indicating that NAFLD leads to cirrhosis development at the same rate as do well-established liver diseases caused by alcohol and HCV [54]. The progression to cirrhosis is a function of inflammation, which correlates with the elevation of liver enzymes: A higher grade of inflammation coincides with a higher serum concentrations of liver enzymes, which in turn denotes a higher degree of fibrosis since inflammation begets fibrosis. In HCV, untreated fibrosis that develops to fully developed cirrhosis and hepatic decompensation complicated by ascites, hepatic encephalopathy, and esophageal varices occurs in ~ 4% of cirrhotic patients/yr or ~18%/5 yr [55]. Nonetheless, there is a paucity of studies documenting cirrhosis development originating in NAFLD. In contrast to NAFLD, patients with NASH and fibrosis are characterized by a rapid and consistent progression to cirrhosis (30% in 5 to 10 years). Since cardiovascular disease and cancer are the most common causes of death in patients with NAFLD, the rate of liver-related (i.e. cardiovascular disease and HCC) mortality is likely to be ~10% within 10 years [56].

US Racial Disparities

Studies relating to US minority populations have demonstrated distinct disparities in the prevalence of NAFLD and NASH by race and ethnicity. The National Institutes of Health defines health disparity as "differences in the incidence, prevalence, mortality, and burden of

diseases and other adverse health conditions that exist among specific population groups in the United States.” NAFLD is the most common reason for elevation of liver enzymes, especially ALT, among all racial groups. Prevalence of ALT elevation varies significantly based on racial or ethnic origin: Hispanics displayed 13.7% ALT rise; non-Hispanic whites, 8.6%; and non-Hispanic blacks, 5.4% [57]. Although NAFLD occurs in both sexes and in all ethnic groups, the average age varies according to ethnicity [58-60]. Several studies indicate that African-Americans have the lowest incidence of this disease whereas Hispanics have the highest incidence with NAFLD occurring at an earlier age [19, 60, 61]. Still, accurate trends in race-specific disparities of incidence, burden of disease, and the overall survival of NAFLD and NASH patients are unknown; the literature is scarce on the underlying etiologic or molecular factors responsible for racial and ethnic differences. Genetic and metabolic factors have been suggested as underlying causes for these differences [28, 62]. The higher prevalence in Hispanics may be attributable to their propensity to have greater adiposity and IR compared to Caucasians [21, 63-65]. Although African-Americans have a higher rate of diabetes and IR compared to Caucasians and Hispanics, their reduced rate of prevalence of NAFLD and NASH may be due to their lower serum concentrations of triglycerides [66]. Nevertheless, there is some evidence that NAFLD prevalence is also affected by age (although it is not known if the cause is duration of the disease or other underlying risk factors for older age), gender (higher in males), and other pathological benchmarks.

A 2009 study of ethnic differences in obesity surgery patients by Kallwitz et al. reported that African-Americans had significantly lower rates of steatosis, NASH and fibrosis score than non-Hispanic whites and hispanics [67]. Yet, African-Americans have one of the highest rates of HCC mortality [68], which may also be due contributing factors other than NAFLD such as HCV infection and greater alcohol consumption.

Population-based studies, even though few have been implemented thus far, provide better appraisals of the prevalence of NAFLD than do conventional clinical studies. There are two studies that provide data regarding the prevalence of NAFLD in the general US adult population including ethnic minority groups: The Dallas Heart Study [63] and the NHANES Survey [34]. The Dallas Heart Study, conducted in 2004, which involved 2,200 adults who were assessed for NAFLD using ultrasound (US) liver imaging reported that 31% exhibited fatty liver disease [63]. Yet, 79% of these US-diagnosed NAFLD patients had no liver enzyme elevation, indicating that liver enzyme elevations are inadequate surrogate markers for the general population, at least in the USA. The Dallas Heart Study also included ethnic groups divided among racial lines: 1100 African-Americans (48.3%), 700 Caucasians / European-Americans (32.1%) and 400 Hispanics (17.5%) in which the prevalence of simple hepatic steatosis varied with ethnicity (Fig. 1). There were also gender disparities in this study revealing that there was no difference in the prevalence of hepatic steatosis between males and females in the African-American and Hispanic populations. Conversely, among the ethnic groups, male Caucasians were overrepresented at 42% compared to females at 24% (see Fig. 1). Several studies report that regardless of methodology used (liver enzymes [ALT and aspartate transaminase (AST)] or ultrasound or magnetic resonance [MR] spectroscopy), the prevalence of NAFLD is much more skewed toward Hispanic patients in the USA. The Dallas Heart Study likewise reported that Hispanics had a higher prevalence of NAFLD (45%) than non-Hispanic whites (33%) or non-Hispanic blacks (24%), with the

latter having the lowest overall prevalence of fatty liver disease [63] (Fig. 1). When Hispanic and black subjects were compared to non-Hispanic white women [69], they exhibited more hypertension, obesity, diabetes and sedentary behavior, all risk factors for cardiovascular disease, which is the #1 cause of death among NAFLD patients.

A similar prospective study based in San Antonio involving a smaller cohort of middle-aged ethnic groups was conducted seven years later at the Brooke Army Medical Center by Harrison and colleagues in 2011 [36]. The overall prevalence of NAFLD in the three ethnic groups studied was 46% (as opposed to 31% in the 2004 Dallas Heart Study) with Hispanics having the largest rate at 58.3%, followed by non-Hispanic whites at 44.6% and non-Hispanic blacks at 35.1%. Furthermore, similar to the Dallas Study, males (58.9%) were more affected with NAFLD than were women (41.1%). Although this was not a population-based study, the San Antonio study revealed that the prevalence of NAFLD and NASH, much higher than was previously estimated in the Dallas Heart study group, is increasing across all racial and ethnic groups [36] (see Fig. 1 for comparison of the prevalence of NAFLD as documented in these two studies). Nonetheless, Hispanic adults have a higher prevalence of NAFLD despite similar rates of MetS for blacks and whites [70], possibly due to a higher concentration of obesity in Hispanic adults, notwithstanding the observation that non-Hispanic black adolescents have a lower prevalence of MetS and NAFLD but a higher concentration of IR [57, 63]. Furthermore, data also reveal a less significant link between IR and elevated ALT in non-Hispanic black adolescents, diminishing the predictive value of IR for ALT elevation in this ethnic group. This also lends credence to ethnic or racial differences in the prevalence of MetS, IR and NAFLD [57]. Why is this difference so stark? The most plausible explanations take into account correlates such as age, triglyceride concentration, and plasminogen-activator inhibitor-1(PAI-1), which are only associated with NAFLD in Hispanics whereas serum adiponectin concentration is reported to be exclusively and independently associated with NAFLD in African-Americans [62]. This does not negate the strong possibility that NAFLD may be influenced by important, yet unrecognized, environmental and genetic factors.

The other much larger study usually incorporated into multiple databases was presented by NHANES, which conducted national surveys and interviews in 2007 to assess the prevalence of NAFLD in the United States. The data from this study determined that when all other factors tested negative, 5.5% of the U.S. population had elevated blood enzyme concentrations, later diagnosed as NASH. The NHANES study of 1999-2010 involving children aged 12-19 (adolescent cohort) divided the children with elevated ALT by ethnicity. The data on all MetS components revealed that Hispanic children have a higher rate of ALT elevation and a higher risk of MetS and IR [71]. The selective measurement of ALT concentration based on race or ethnicity underscores the lack of effective surrogate markers for NAFLD / NASH in the absence of biopsy. The dilemma lies in standardizing alternative diagnostic mechanisms for the accurate diagnosis of fatty liver disease across all racial lines. Clinicians usually start the diagnosis process based on which known risk factors are involved. The homeostatic model assessment for insulin resistance (HOMA-IR), which is a measure of IR and β -cell function, can be a good predictor of ALT concentration for Hispanic patients but not for non-Hispanic blacks. The same is true for waist circumference. Interestingly, the most robust predictor of fatty liver for non-Hispanic black children is an

elevated plasma triglyceride (TG) concentration, which is lower in this group than in other ethnic groups because non-Hispanic blacks have less hepatic lipid content, lower plasma lipoprotein lipase (LPL), and less overall liver disease [3, 72]. Why are blacks at an advantage and Hispanics at a disadvantage? In addition to genetic factors, there may also be social health determinants that influence the natural history of NAFLD and treatment outcome in Hispanics when compared to other ethnic groups. These may include difficulty in accessing and utilizing the healthcare system, possible language barriers, low rates of medical insurance coverage, low income, and limited knowledge of health services and health resources. The two population-based studies (Dallas and NHANES) report that NAFLD prevalence, which is 5.5 -31% in the US, is estimated to be significantly more common than hepatitis C infection [50, 73]. One cautionary note here is that the measurable value of liver enzymes is reduced when blood samples are frozen, thereby underestimating their activity.

In the US, South Asians have more IR than Caucasians despite having equal or lower BMI [49, 74]. Because of this, there are different criteria to define MetS between Western and Asian countries. Male Asians have lower central obesity index (>90 cm) compared to Western males at >102 cm. Their waist circumference and IR are also lower than their Western counterparts. Furthermore, fasting glucose concentrations for Asians generally exceed 100 mg/dl whereas for Westerners it exceeds 110 mg/dl [49, 74]. Furthermore, Asian-Indian men have more liver fat content and have more IR than BMI- and age-matched white individuals [75, 76]. Likewise, Asian Indians have a lower normal BMI range (18.5 -22.9 as opposed to 18.5 – 24.9 for Westerners). Their overweight measurement is also lower at 23-24.9 compared to the West's 25-29.9. Obesity is defined as BMI ≥ 30 for Westerners and ≥ 25 for Asian Indians [49, 74]. American Indians and Alaskan natives who have higher BMI and waist circumference have a NAFLD prevalence rate of 0.4 - 2%, which is lower than in other ethnic groups although based on relatively small datasets (Table 1) [77, 78]. It is possible that two patients with the same BMI can have differing subcutaneous fat, visceral, or truncal fat distributions, any of which may be more pathophysiologically important in one of the patients than in the other. Adipose tissue, highly metabolically reactive, is associated with augmented inflammatory signaling and insulin with resistance. Non-Hispanic blacks, for example, controlling for age and adiposity, have more lower extremity fat and less visceral fat [63, 64]. Therefore, there is a pressing need to define the concentration of triglycerides (TG) which best reflects the presence of IR for each ethnic group, especially in non-Hispanic blacks where IR is predicted based on a normal plasma TG concentrations. Accurate diagnosis requires the establishment of ethnic-specific thresholds for triglyceride concentrations [3].

Genetics

Recently published reports indicate that genetics underlie ethnic differences. Genes associated with NAFLD include neurocan (*NCAN*), which may have a protective effect for Hispanics but increases the risk of steatosis for non-Hispanic blacks and lysophospholipase like 1 (*LYPLAL1*), glucokinase (hexokinase 4) regulator (*GCKR*), and protein phosphatase 1 regulatory subunit 3B (*PPP1R3B*), which may confer increased risk for hepatic steatosis although correlations of these genes with serum lipid profiles in are sparse [79]. *GCKR* is

reported to be closely associated with NAFLD in populations of Chinese origin [80], whereas Patatin-like phospholipase domain-containing 3 (*PNPLA3* or adiponutrin), has emerged as the genetic factor predisposing Hispanics more at risk for fatty liver disease. Transmembrane 6-superfamily member 2 (*TM6SF2*), discovered in an exome-wide association study of liver fat content, is also associated with hepatic steatosis. Although *TM6SF2* is associated with NASH, advanced fibrosis, and a loss-of-function mutation in VLDL secretion, its precise contribution to NASH pathogenesis has not been delineated [28]. Nonetheless, its mutation is associated with elevated ALT, hepatic steatosis, and lower concentration of alkaline phosphatase, LDL and triglycerides. This gene is most prevalent in individuals of European ancestry and less in Hispanics and African-Americans [81].

Conclusions

The growing epidemic of obesity and sedentary lifestyle will continue to increase the prevalence and impact of NAFLD, making its pernicious form, NASH, potentially the most common cause of advanced liver disease and mortality in the world. A legitimate concern is that the disease burden of NAFLD is widely underestimated even among African-Americans. To establish the severity of fatty liver disease, liver biopsy still remains the “gold standard” and most reliable approach for confirmation, diagnosis and staging of NAFLD and especially NASH, although recent imaging techniques are making inroads and will be indispensable for population-based studies. Future predictive and diagnostic models for NAFLD and NASH will be developed to assist in obtaining more reliable data at a population level.

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Key Findings and unmet needs

- The prevalence of NAFLD, increasing among all ethnicities, parallels the epidemics of diabetes and obesity.
- Precise epidemiological data with newer non-invasive biomarkers for NAFLD and NASH will provide more accurate information about the true burden of disease of this common chronic liver disease.
- Clinicians should have a low threshold for screening patients with T2DM, MetS, or IR for NAFLD/NASH, in particular if there is concern for advanced fibrosis.

Fig. 1. Comparison of prevalence of fatty liver in the Dallas Heart study of 2004 [63] with the San Antonio Study of 2011 [36] . NHW = Non-Hispanic White NHB = Non-Hispanic Black

Table 1

The Prevalence of NAFLD and NASH in countries around the World

Location	NAFLD [References]	NASH [References]	Children / NAFLD
World	4-46% [13, 49, 82, 83]	3-5% [13, 49, 82, 83]	n.r.
Western Countries	20-40% [84-86]	2-3% [53]	n.r.
Eastern Countries	10-20%	n.r.	n.r.
Africa	n.r.	n.r.	n.r.
Nigeria	9% [87]	n.r.	n.r.
Sudan	20% [87]	n.r.	n.r.
Asia	15-30% [88-91]	n.r.	n.r.
China	15-30% [24, 49, 92]	n.r.	4-5.2% [93-96]
Japan	9-30% [20, 97, 98]	n.r.	4-5.2% [93-96]
South Korea	18% [49, 89, 98]	n.r.	4-5.2% [93-96]
[99] Hong Kong	16% [49]	n.r.	n.r.
India	16-32% [100]	n.r.	n.r.
Indonesia	30% [49]	n.r.	n.r.
Malaysia	17% [49, 98]	n.r.	n.r.
Pakistan	18% [101]	n.r.	n.r.
Singapore	5% [49]	n.r.	n.r.
Taiwan	11-41% [49]	n.r.	n.r.
Australia	20-30% [102, 103]	n.r.	n.r.
Europe	25% [104]	n.r.	2.6-10% [104]
Greece	31% [105]	40% [105]	n.r.
Italy	23% [106]	n.r.	n.r.
Middle East	20-30% [106-108]	n.r.	n.r.
Iran	4.1% [109]	n.r.	2.9% [109]
Israel	30% [110]	n.r.	n.r.
Saudi Arabia	16.6% [111]	n.r.	n.r.
Latin America	17-33.5% [99]	n.r.	n.r.
Mexico	16% [112]	n.r.	n.r.
Venezuela	n.r.	n.r.	39% [113]
North America	n.r.	n.r.	n.r.
USA	27-34% [13, 41, 47, 114]	3-5% [13]	10-20% [48]
African-Americans	24% [63]	n.r.	n.r.
American-Indian	0.4-2% [77]	n.r.	n.r.
European-Americans	33% [63]	n.r.	n.r.
Hispanics	45% [63]	n.r.	n.r.
Native-Alaskan	0.4-2% [78]	n.r.	n.r.
Canada	7% [115]	3% [115]	n.r.

n.r. = not reported

Table 2

Prevalence rates of nonalcoholic fatty liver disease from population-based studies (adapted in modified form from Pan et al. [116]).

Study Population	Number of Subjects	NAFLD Diagnosis	Reference	Prevalence of NAFLD			
				Overall	NHW	Hispanic	NHB
NHANES III (1988-1994)	5724	ALT ¹	Ruhl et al [117]	2.8%	2.6%	8.4%	1.9%
NHANES III (1988-1994)	15676	ALT or AST ²	Clark et al [19]	5.4%	4.8%	9.9%	4.2%
NHANES III (1988-1994)	11613	US ³	Younossi et al [118]	18.8%	NA	NA	NA
NHANES (1999-2002)	6823	ALT ⁴ or AST ⁴	Ioannou et al [119]	8.1%	NA	NA	NA
Dallas Heart Study	2287	MRS ⁵	Browning et al [63]	31%	33%	45%	24%
NHANES III (1988-1994)	12454	US ³	Lazo et al [34]	NA	NA	NA	13.5%
NHANES III (1988-1994)	3846	US ³	Smits et al [120]	30.2%	29.8%	39.4%	23.1%
NHANES III (1988-1994)	9675	US ³	Schneider et al [121]	12.5%	21.2%	11.6%	NA

¹ ALT > 43 U/L

² ALT > 40 U/L and AST > 37 U/L for men; ALT and AST > 31 U/L for women

³ Ultrasound

⁴ ALT > 43 U/L or AST > 40 U/L. NHANES: National Health and Nutrition Examination Survey

⁵ Hepatic triglyceride content > 5.5%;

NAFLD: Nonalcoholic fatty liver disease; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; US: ultrasonography; MRS: Magnetic resonance spectroscopy; NHW: Non-Hispanic Whites; NHB: Non-Hispanic Blacks.

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Table 3

Description of all adolescents (12-19 years) in sample, NHANES 1988-1994 to 2007-2010 (adapted from Welsh et al. [122])

Characteristic	1988-1994 N = 2748	1999-2002 N = 4004	2003-2006 N = 3824	2007-2010 N = 2138	P Value
Age (years)	15.4 (0.1)	15.5 (0.1)	15.5 (0.1)	15.5 (0.1)	0.43
Gender, (% Male)	51.0 (1.8)	51.4 (1.0)	51.8 (1.1)	52.1 (1.2)	0.61
NHW (%)	67.1 (2.4)	58.9 (2.0)	63.0 (2.8)	58.9 (2.8)	0.13
NHB (%)	14.7 (1.3)	14.2 (1.7)	15.2 (1.8)	14.2 (1.2)	0.99
Hispanic (%)	8.6 (1.0)	10.9 (1.4)	11.6 (1.5)	13.6 (1.9)	0.02
Other (%)	9.5 (1.6)	16.1 (2.1)	10.2 (1.1)	13.3 (1.7)	0.77
Overweight	15.9 (1.0)	15.8 (0.8)	17.6 (0.9)	17.7 (1.0)	0.09
Obese	11.2 (1.0)	18.1 (0.8)	19.2 (1.3)	20.0 (1.1)	<.0001
BMI (z-score)	0.38 (0.03)	0.54 (0.03)	0.60 (0.04)	0.64 (0.03)	<.0001

NHW = Non-Hispanic White
NHB = Non-Hispanic Black