

A Fatty World: Exploring Racial Disparity in NAFLD/NASH

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Abstract

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Background: Nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH) are metabolic disorders that affect the liver. A world crisis is unfolding as the number of people with NAFLD/NASH is substantially increasing. Chronic liver disease is now estimated to be the leading cause for liver transplant. Studies have shown that NAFLD/NASH is often more pronounced in certain ethnic populations, particularly Asian and Hispanic communities. An explanation for this increased incidence may be associated with intrinsic ethnic factors and/or genetic polymorphism (variants in a particular DNA sequence). Further, the etiology of NAFLD/NASH is also linked to obesity, diabetes, and other risk factors which are highly pronounced in racial communities. Unfortunately, there currently is no NAFLD/NASH-specific medication on the market to treat these diseases. New drug development and ongoing research is necessary to treat and cure NAFLD/NASH, with particular attention given to engage high-risk populations. Importantly, the discovery of new treatments may be beneficial with ongoing support and collaboration between the research community and ethnic groups.

Conclusion: For NAFLD/NASH clinical studies, participation of Asians and Hispanics is vital and may be important in drug development programs for successful and targeted treatment.

Keywords: NAFLD; NASH; Polymorphism; Variants; Ethnic

Abbreviations: Body mass index (BMI); Genome-wide associated (GWA); Glucokinase regulatory protein (GCKR); Japanese Society for the Study of Obesity (JASSO); Magnetic resonance elastography (MRE); Magnetic resonance imaging (MRI); National Health and Nutrition Examination Survey (NHANES); Neurocran (NCAN); Nonalcoholic fatty liver disease (NAFLD); Nonalcoholic steatohepatitis (NASH); Patatin-like phospholipase 3 (PNPLA3); Transmembrane 6 superfamily member2 (TM6SF2); World Health Organization (WHO)

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Citation: Jaycox SH. A Fatty World: Exploring Racial Disparity in NAFLD/NASH. J Hep. 2016, 2:2.

Received: October 07, 2016; **Accepted:** December 03, 2016; **Published:** December 07, 2016

Introduction

Several metabolic diseases as well as their associated underlying risk factors have been found to be more pronounced in selective ethnic communities. For example, in the United States (US) type 2 diabetes is more prevalent in African and Native Americans than Caucasians [1]. In addition, obesity is highly widespread among both African American and Hispanic groups. This point was emphasized in a recent publication that described nearly half of African Americans (48%) and Hispanics (43%) in the

US are categorized as obese [2]. Many of these race-related differences are derived from intrinsic ethnic factors and/or genetic polymorphism (variants in a particular DNA sequence). A similar trend has arisen for liver metabolic disorders such as non-alcoholic fatty liver disease (NAFLD). This overview will highlight the prevalence of NAFLD and the associated risk factors within ethnic populations from a national and global perspective.

NAFLD/NASH

NAFLD, a broad spectrum of liver manifestations is histologically

subdivided into simple steatosis, nonalcoholic steatohepatitis (NASH), and cirrhosis. NAFLD is a silent metabolic disease that may be suspected after a patient's blood tests show elevated liver enzyme levels. A physician may order a number of tests such as an ultrasound after the abnormal lab test to verify the disease. Magnetic resonance imaging (MRI) and magnetic resonance elastography (MRE) are imaging tools used to determine if the disorder is due to NAFLD. Lastly, the gold standard and most invasive procedure, the liver biopsy, can be used to confirm a diagnosis [3].

NASH a detrimental form of the disease, often progresses to cirrhosis and hepatocellular carcinoma, and is estimated to become the leading cause of liver transplantation in the US by 2020 [4]. NASH is characterized by steatosis, liver inflammation and injury with or without fibrosis. Although still unknown, the etiology of this fatty liver pathology is strongly associated with obesity, insulin resistance and dyslipidemia. NAFLD is also often predicted by an increased body mass index (BMI), waist circumference, and waist-to-hip ratio [5]. Additional risk factors may include a family history of diabetes, cardiovascular diseases, metabolic syndrome, and high blood pressure [6].

An Upward Trend

NAFLD has emerged as a major public health issue and is the most common cause of liver disease in Western countries, affecting up to 20–35% of the general population [4]. The National Health and Nutrition Examination Survey (NHANES), a large and representative survey of the US population reported the prevalence of fatty liver disease in adults (aged 20–74 years) increased from 18% in 1988-1991, to 29% in 1999-2000, and to 31% in 2011-2012 [7]. Along with the growing occurrence of obesity, type 2 diabetes, and metabolic syndrome, these data reflects how the incidence of NAFLD has increased steadily over the last few decades.

Recent studies show that there is a higher prevalence of NAFLD in individuals who are obese and have type 2 diabetes. Additionally, NAFLD prevalence can be more than 70% in obese adults with type 2 diabetes [8]. Research also shows that having both NAFLD and diabetes increases the risk of moderate to severe fibrosis by 65% [9]. Furthermore, the presence of both NAFLD and diabetes may lead to an increase severity of chronic illness such as cardiovascular diseases or other metabolic derangements.

Currently, there is an estimated 1 billion people worldwide affected by NAFLD [10]. In this respect, NAFLD is no longer considered a disease exclusive to developed Western countries, as the frequency of this metabolic disorder is also increased in developing countries; with an estimated prevalence of nearly 10% in developing nations [11]. Additionally, the prevalence of NAFLD is expected to increase by 50% by 2030 [12]. Furthermore, NAFLD is now widely recognized as the next big global epidemic. Moreover, these numbers are largely influenced by a booming incidence within certain ethnic classes.

NAFLD and Ethnicity

Although NAFLD reaches every corner of the world due to increased rates of obesity and insulin resistance, two ethnic

groups especially stand out for their high risk of fatty liver disease, mainly those of Asian and Hispanic descent. In China and Japan, the prevalence of NAFLD has reached epidemic proportions [1] and is rising in many other Asian-Pacific communities as well [13]. NAFLD prevalence in the Asian population may be secondary to the rising rate of obesity. Importantly, according to the World Health Organization (WHO) and the Japanese Society for the Study of Obesity (JASSO), waist circumference and BMI cutoff values associated with increased metabolic risk are adjusted for race (Table 1). A critical consideration since Asian populations demonstrate greater risk for fat-related disorders such as NAFLD, heart disease and diabetes when comparing Asians and Caucasians of the same anthropometric measurements (weight and height) [14]. Fan and Farrell, reported the prevalence of fatty liver in the general population of East and South China (two densely populated regions) were 17% and 15%, respectively [15]; of which, nearly 90% of the fatty liver cases appeared to be related to metabolic factors such as NAFLD. Furthermore, the rate of NAFLD in Central China has doubled in the past 7–10 years; it has increased from 13% to 25% [15]. Alarmingly, in a Korean study in which liver biopsies were performed on 589 consecutive potential liver transplant donors, NAFLD prevalence was exhibited in 51% of the donors [16]. Altogether, the data reflects the severity of NAFLD within the Asian populations (Table 2).

The disparity in NAFLD prevalence in diverse ethnic groups may be explained by the different rates of metabolic syndrome and underlying factors in those ethnicities; in the US 22 % of African Americans, 24% of non-Hispanic Whites and, 32% of Mexican Americans develop metabolic syndrome [17]. Similar trends have been reported for the incidence of NAFLD in the same ethnic

Table 1 Obesity Standards for BMI and Waist Circumference

Group	BMI	Waist circumference (inches)	
		Male	Female
Asian	>28 kg/m ²	≥35 (90 cm)	≥31 (80 cm)
Non-Asian	>30 kg/m ²	≥40 (102 cm)	≥35 (88 cm)
Japanese	>25 kg/m ²	≥33 (85 cm)	≥35 (90 cm)

Table 2 Prevalence of NAFLD in Western and Asian Pacific Countries.

Country	NAFLD (%)	Reference
Western Countries		
Italy	20%	[9]
Spain	33.4%	[9]
Mexico	17%	[35]
Chile	22%	[35]
Romania	8%	[9]
Greece	31%	[9]
Asian-Pacific Countries		
Japan	9-30%	[36]
China	5-24% (highest % found in urban area)	
India	5-28%	
Indonesia	30%	
Malaysia	17%	
Korea	18%	
Singapore	5%	

Percent ranges are determined by the region and development.

groups whereas it is: 13.5% for African Americans, 18% for non-Hispanic Whites and, 24% for Hispanics [18] A global prevalence of NAFLD is illustrated in (Table 3).

One theory suggests that these differences in NAFLD by race may be attributed to the distribution of adipose tissue or serum triglyceride levels. This stems from observational studies showing that despite increased insulin resistance in African Americans, there is a relatively lower risk of developing NAFLD/NASH, due to less visceral adipose tissue and lower triglycerides than Hispanics, a phenomena coined the 'insulin resistance paradox' [19]. On the other hand, a number of studies have found that NAFLD prevalence in the Hispanics population is secondary to the high consumption of carbohydrates, which impact liver metabolism [18]. Histologic and serologic properties of NAFLD in different ethnic groups were reflected in a retrospective analysis of liver biopsies which revealed that Hispanics displayed greater liver damage [20]. In addition, the analysis also revealed more pronounced hepatocyte damage and more advanced fibrosis than non-Hispanic Whites or African Americans [20]. Additionally, a more prominent inflammatory status is also considered a contributing factor for Hispanics with NAFLD due to higher levels of liver function enzymes such as aminotransferases [20]. Taken altogether the risk factors noted above have led to both Hispanic men and women exhibiting a chronic liver disease rate that is twice that of the Caucasian population [17].

Genetic Factors Associated with NAFLD/NASH

With a growing focus on epigenetic and genome-wide associated (GWA) studies, researchers have established that ethnic variations in NAFLD prevalence may arise from a genetic susceptibility. In particular, a polymorphism in the patatin-like phospholipase 3 (PNPLA3) gene, which encodes the enzyme adiponutrin, a regulator of hepatic fat content and lipid secretion, has been implicated in the development of NAFLD/NASH [21]. Specifically, the *PNPLA3* I148M rs738409 variant has been suggested to be a major determinant of race-related differences in hepatic fat accumulation, independent of insulin resistance and serum lipid concentrations across multiple ethnicities [4, 21, 22]. Similar to NAFLD/NASH incidence rates, Hispanics (49%) demonstrated the highest frequency of the I148M polymorphism, followed by non-Hispanic Whites (23%), and African Americans (17%) [19, 21]. According to a meta-analysis review of 23 studies the *PNPLA3* gene has a higher frequency in Hispanic (69.0%) followed by the Asian population 54.2% and 42.2% for the Caucasian populations. [3] In addition, several studies have also established that the I148M variant contributes to fibrogenesis in the development of NASH and cirrhosis [23]. Moreover, polymorphisms within *PNPLA3* have

also been associated with the advancement of NAFLD/NASH, and cardiovascular risk profiles in Chinese [24], Japanese [25], and Asian Indian [26] cohorts (Table 4). Other genes of interest with racial significance associated with NAFLD/NASH are *GCKR*, *TM6SF2*, and *SAMM50* [18, 27, 28] (Table 4). Taken altogether, intrinsic genetic factors such as body habitus and genetic variants with gene expression within the Asian and Hispanic cohorts have identified these two ethnic groups as high-risk populations for the development of NAFLD/NASH.

Ethnicity and NAFLD/NASH therapy

There currently are no NAFLD-specific therapeutic agents available on the market; however, a number of insulin sensitizers, antioxidants and new investigational products are being developed for the treatment of NAFLD/NASH. Two landmark studies in this domain have shown promising results, the Farnesoid X Receptor (FXR) Ligand Obeticholic Acid in NASH Treatment (FLINT) study and the Pioglitazone versus Vitamin E versus Placebo for the Treatment of Nondiabetic Patients with Nonalcoholic Steatohepatitis (PIVENS) studies. Obeticholic acid, a farnesoid X nuclear receptor ligand was investigated in non-cirrhotic NASH subjects in the multicenter, FLINT study with the primary outcome to improve histological liver features. This randomized placebo-controlled study of 283 participants constituted mainly of a Caucasian demographic with only 6% Asians, and 15% reported as being of Hispanic ethnic origin [29]. The value of self-reported ethnicity for the Hispanic population is also similar for the PIVENS study, a phase 3, multicenter study which examined the effect of pioglitazone versus vitamin E compared to placebo in NASH subjects [30]. The PIVENS study showed evidence that insulin sensitizers such as pioglitazone may be a useful therapeutic agent for individuals with both insulin resistance and NASH. However, this type of therapy may benefit Asians and Hispanics over African American as an anti-NASH treatment due to the insulin resistance paradox as discussed above. [17, 18]. Nonetheless, future ethnic-based studies may validate the benefit on the various subpopulations.

The lack of drugs to treat NAFLD/NASH and the increasing world crises necessitates ongoing research, specifically in the high risk groups; unfortunately, participation of ethnic groups in clinical research has always been historically low [31]. In part, this may be related to several social and cultural impediments that have limited inclusion of disparate groups within clinical studies [32]. Nonetheless, the potential contribution of a subject's genetic makeup with respect to drug development and metabolism must be taken into consideration, a statement that was echoed by the National Pharmaceutical Council and National Medical Association [33]. Moreover, pharmaceutical and biotech companies are increasingly cognizant of the diversity, as they work to find treatments. Importantly, as NAFLD/NASH therapies are developed it may be in the best interest of all stakeholders to conduct those clinical studies on disparate groups of subjects, particularly those identified as Hispanic and Asian. Furthermore, minority inclusivity was emphasized by the Food and Drug Administration when they published the Demographic Rule in 1998, a regulatory guidance for pharmaceutical companies to report and tabulate clinical study data by race and ethnicity [34].

Table 3 Global Prevalence of NAFLD in High-risk Ethnic Populations.

Group	Obesity %	Dyslipidemia %	Diabetes %	Reference
Japanese	50- 80%	42-58%	40-50%	[36]
Chinese	70-80%	57%	35%	[36]
Mexican	26%	28%	24.1	[37,38,39]
African American	29%	3%	12.5	[38,39]
Singaporean	10.8%	17.4%	11.3%	[40]

Table 4 Single nucleotide polymorphism (SNP) associated with NAFLD/NASH

Gene	Allele	Position	SNP	Ethnicity	Associations	Reference
PNPLA3	G	I148M	rs738409	MA	Liver steatosis Triglyceride levels	[41]
PNPLA3	G		rs738409	NHW	Hepatic Steatosis with high ALT level Higher triglycerides Higher cholesterol Lower levels of HDL	[21] [28]
PNPLA3	G		rs738409	Argentinian Japanese Italian Hispanic	Increased ALT and AST level Decreased levels of triglycerides	[42]
PNPLA3	T	S453I	rs6006460	AA	Lower Hepatic Fat Reduced triglycerides Increased HDL	[21]
NCAN	T	P92S	rs2228603	NHW	Hepatic Steatosis with high ALT level Lower triglycerides and plasma LDL-cholesterol	[21]
GCKR	T	P446L	rs780094	Asian	Increased Triglyceride concentration	[43] [44]
GCKR		APOC3	rs1260326	NHW AA Hispanic	Elevated triglycerides Elevated triglyceride Large VLDL	[30] [45]
TM6SF2	T	E167K	rs58542926	Chinese	Hepatic Steatosis Fibrosis Regulates total cholesterol levels and myocardial infarction risk	[46] [47]

Abbreviations: African American (AA), Glucokinase regulatory protein (GCKR), Mexican America (MA), Neurocran (NCAN), non-Hispanics Black (NHB), non-Hispanic white (NHW), Protein phosphatase 1 regulatory subunit 3b (PPP1R3B), Transmembrane 6 superfamily member2 (TM6SF2), Very Low-density lipoprotein (VLDL).

Conclusion

NAFLD and NASH are a spectrum of liver disease recognized as a growing phenomenon, slated to become the leading cause for liver transplant by 2020 [4]. Metabolic diseases which include diabetes, as well as NAFLD and NASH are prevalent in select disparate communities. African and Native American communities are at greater risk for diabetes and NAFLD/NASH has predominance in the Asian and Hispanic ethnicities. The incidence of NAFLD/NASH in minority groups can be linked to genetic-predisposition, metabolic risk factors, environmental factors, and culture. As NAFLD/NASH becomes increasingly recognized as a global health issue, therapies will need to be developed. During the drug discovery process ethnicity should be taken in account with both pharmacogenomics and pharmacological consideration given to

the populations identified as high risk. Unfortunately historical distrust for the medical system has led to a lack of minority participation in clinical studies. It will therefore be imperative for research organizations to identify ways to gain the trust and participation from high-risk populations so that they are involved in this critical drug discovery process. Perhaps, a solution to this may be collaborations between pharma and culturally specific groups, agencies, and/or organizations. These alliances may prove advantageous while developing NAFLD/NASH drugs and treatments as, these relationships foster partnerships and trust.

Competing and conflicting Interests

SHJ is an employee of Celerion Inc.

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