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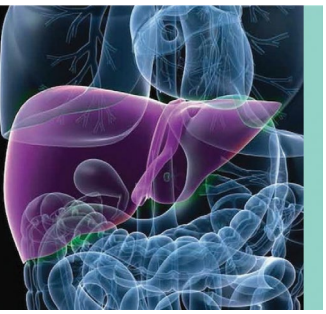

Racial Disparities in Diagnosis and Prognosis of Nonalcoholic Fatty Liver Disease

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Nonalcoholic fatty liver disease (NAFLD) is defined as a spectrum of diseases, including simple steatosis to nonalcoholic steatohepatitis (NASH), with or without fibrosis and cirrhosis, that occurs in the absence of significant alcohol consumption and after exclusion of other etiologies of liver disease.[1] About 25% of the world's population is known to have some form of NAFLD. The incidence of NAFLD has continued to increase worldwide, with the parallel rise of obesity and metabolic syndrome, particularly in western countries.[1,2] NASH has now emerged as one of the leading causes of chronic liver disease, cirrhosis, and hepatocellular carcinoma (HCC).[3]

There is a significant racial disparity in the prevalence of NAFLD in the United States, with a disproportionately higher predilection for Hispanics/Latinos.[4] In a recent systematic review and meta-analysis, Rich et al.[5] showed significant racial disparities in NAFLD prevalence and severity in the United States, with the highest proportion in Hispanics and the lowest burden in blacks. Recent epidemiological study showed that the mortality rates for NAFLD-cirrhosis and HCC have increased in non-Hispanic whites followed by Hispanics and non-Hispanic blacks.[6] In this review, we focused on the racial differences in the diagnosis and prognosis of NAFLD.

RACIAL DISPARITIES IN THE PREVALENCE OF NAFLD/NASH

NASH is estimated to affect 3% to 5% of the global population. Estes et al.[7] recently reported that in the United

Abbreviations: ALT, alanine aminotransferase; APRI, AST/platelet ratio index; AST, aspartate aminotransferase; CK-18, cytokeratin 18; CT, computerized tomography; FIB-4, Fibrosis-4; HCC, hepatocellular carcinoma; MRI, magnetic resonance imaging; N/A, information not available; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; NFS, NAFLD fibrosis score; NHANES, National Health and Nutrition Examination Survey; SNP, single-nucleotide polymorphism; T2D, type 2 diabetes.

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States, NAFLD is likely to increase from 83.1 million (2015) to 100.9 million by 2030, and NASH from 16.52 million (2015) to 27 million.

A meta-analysis in 2018 composed of 34 studies reported that NAFLD prevalence was highest in Hispanics, intermediate in whites, and lowest in blacks. There was a wide variation in NAFLD prevalence rates among studies, ranging from 6.6% to 46.0%.[5] Among patients with NAFLD, risk for progression to NASH was higher in Hispanics (relative risk, 1.09; 95% confidence interval, 0.98–1.21) and lower in blacks (relative risk, 0.72; 95% confidence interval, 0.60–0.87) than whites. However, the proportion of patients with significant fibrosis did not significantly differ among racial groups. Prevalence appeared to depend on the method of NAFLD diagnosis, with the highest prevalence reported in studies using ultrasound or magnetic resonance imaging (MRI).

In a meta-analysis done in 2005 that included 742 patients with chronic liver disease, Hispanics (28%) had higher prevalence rate of NAFLD compared with Asians (18%), African Americans (3%), and other races (6%).[8] Wagenknecht et al.[9] used computerized tomography (CT) to assess liver/spleen density ratio and abdominal fat distribution to establish that prevalence rates in Hispanic Americans and African Americans were 23% and 10%, respectively. Trico et al.[10] used MRI for quantifying hepatic fat and demonstrated the prevalence rates of NAFLD were 42.9% in whites, 15.7% in blacks, and 59.6% in Hispanics. Mohanty et al.[11] retrospectively examined liver biopsies of 238 patients and showed higher rates of Mallory bodies in Hispanics, hepatic ballooning in Asians, and lower degree of steatosis in blacks compared with whites. Although most studies agree that prevalence of NAFLD is lowest in blacks and highest in Hispanics, some demonstrate variability in the prevalence of NAFLD when comparing whites with Hispanics. The reason for this variation may be related to geographical and diagnostic methodological differences. Table 1 summarizes the findings of these prevalence studies.

DISPARITIES IN THE DISTRIBUTION OF METABOLIC RISK FACTORS AND NAFLD

Obesity, type 2 diabetes (T2D), and hyperlipidemia are major risk factors for NAFLD as seen in Fig. 1. T2D was shown to increase risk for NAFLD and NASH in whites compared with blacks.[12] Distribution of metabolic factors and susceptibility to metabolic factors varies between races. However, despite similar prevalence of T2D and obesity among blacks compared with whites, the latter group has significantly higher risk for NAFLD.[13,14] Browning et al.[12] compared biopsy-proved NAFLD and its progression between black and white patients with severe obesity stratified by the presence or absence of T2D. Whites were significantly more likely than blacks to have NAFLD, NASH, and advanced fibrosis. T2D was associated with increased odds of NAFLD, NASH, and advanced fibrosis in whites only ($P < 0.05$). Also, a higher proportion of blacks than whites with T2D were free of NAFLD (58% versus 22%; $P < 0.01$).

As per National Health and Nutrition Examination Survey (NHANES) data, NAFLD risk, body mass index, and waist circumference were lower in Asian Americans compared with non-Hispanic whites.[15] Bril et al.[16] compared African American patients with Caucasian patients and reported a lower intrahepatic triglyceride content and the presence of NAFLD in African Americans (25.0% versus 51.9%), but the prevalence rate of NASH was not different between ethnicities (57.1% vs. 73.3%; $P = 0.12$). Moreover, they showed similar severity in each of the individual histological parameters (inflammation, ballooning, and fibrosis).

DISPARITIES IN LIFESTYLE AND SOCIODEMOGRAPHIC FACTORS

Lifestyle and sociodemographic factors play an important role in the disparities of NAFLD. In a San Antonio heart study, Mexican Americans consumed increased carbohydrates and saturated fats compared with Anglo-Americans, but there was no impact of socioeconomic status among different ethnicities on consumption of atherogenic diet.[17] Although many genetic factors play an important role in the pathophysiology of NAFLD, physical inactivity, excessive sugar, and decreased vegetable consumption can influence the association of genetic factors and NAFLD.[18] Davis et al.[19] showed that Hispanic children carrying the GG genotype of the *PNPLA3* gene are susceptible to increased hepatic fat when dietary carbohydrate intake was high. Having health insurance or doing shift work did not have any association with increased risk for NAFLD.[20]

TABLE 1. STUDIES DEMONSTRATING DISPARITIES IN NAFLD PREVALENCE

Author/Year	Study Design	Method of NAFLD Diagnosis	NAFLD Prevalence, n (%)					
			Overall	White	Black	Hispanic	Asian	Other
Weston et al. (2005)[8]	Cross-sectional	Imaging (ultrasound, CT) Laboratory tests Biopsy	159 (21.4)	71 (N/A)	5 (N/A)	45 (N/A)	28 (N/A)	10 (N/A)
Lazo et al. (2013)[40]	Cross-sectional	Imaging (ultrasound)	2366 (19)	421 (17.8)	319 (13.5)	570 (24.1)	N/A	N/A
Wagenknecht et al. (2009)[9]	Cross-sectional	Imaging (CT) Laboratory tests Glucose tolerance	224 (19.6)	N/A	22 (10)	54 (24)	N/A	N/A
Trico et al. (2018)[10]	Cohort	Imaging (MRI) Genotyping Glucose tolerance	209 (41.6)	82 (42.9)	21 (15.7)	106 (59.6)	N/A	N/A
Patel et al. (2018)[41]	Retrospective Case-control	Biopsy	76 (19.0)	55 (N/A)	9 (N/A)	4 (N/A)	2 (N/A)	6 (N/A)
Mohanty et al. (2009)[11]	Cross-sectional	Imaging Laboratory tests Biopsy	238 (34.8)	154 (N/A)	36 (N/A)	32 (N/A)	16 (N/A)	N/A
Birerdinc et al. (2012)[42]	Cross-sectional	Laboratory tests (aminotransferases)	1782 (9.6)	1247 (14.0)	131 (6.4)	314 (14.0)	N/A	N/A
Browning et al. (2004)[43]	Cross-sectional	Imaging (MRI)	687 (30.7)	242 (33.0)	265 (24.0)	180 (44.9)	N/A	N/A
Kim et al. (2013)[44]	Cross-sectional	Imaging (ultrasound)	94 (28.3)	47 (36.2)	47 (23.4)	N/A	N/A	N/A
Loomba et al. (2015)[45]	Cross-sectional	Imaging (MRI)	26 (21.7)	18 (19.1)	N/A	5 (27.8)	N/A	N/A
North et al. (2012)[46]	Cross-sectional	Imaging (CT)	181 (6.6)	159 (7.2)	22 (4.3)	N/A	N/A	N/A
Reddy et al. (2013)[47]	Cross-sectional	ICD-9 codes	32,347 (10.7)	20536 (11.8)	2798 (5.8)	4135 (11.4)	N/A	N/A
Tison et al. (2015)[48]	Cross-sectional	Imaging (CT)	706 (17.3)	229 (15.2)	138 (11.2)	259 (27.1)	N/A	N/A
Williams et al. (2011)[49]	Cross-sectional	Imaging (ultrasound) Biopsy	151 (46.0)	91 (44.4)	13 (35.1)	42 (58.3)	N/A	N/A
Younossi et al. (2012)[50]	Cross-sectional	Imaging (ultrasound) Laboratory tests (aminotransferases)	2492 (21.5)	1885 (12.2)	211 (6.6)	190 (12.6)	N/A	N/A

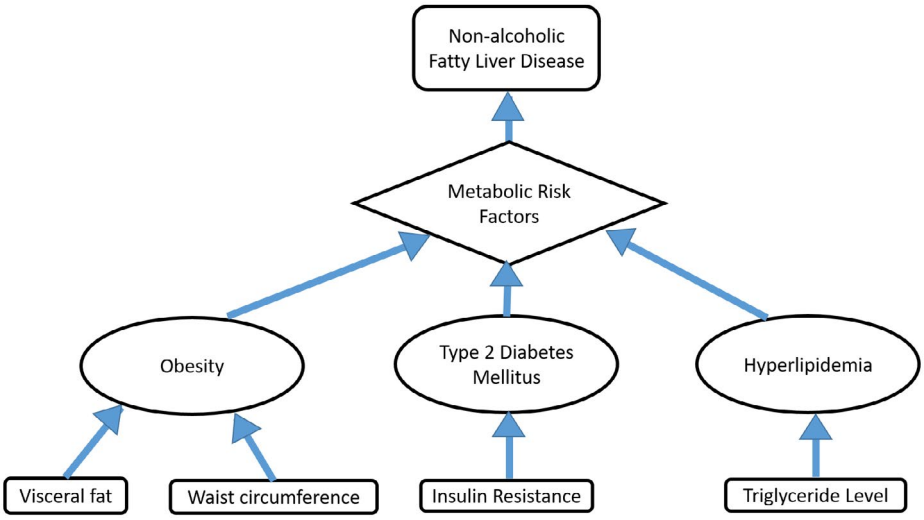

FIG 1 Metabolic risk factors for NAFLD. Among others, these risk factors, such as obesity related to visceral fat and waist circumference, insulin resistance as a result of T2D, and hyperlipidemia related to elevated triglyceride levels, have been shown to differ among races.

DISPARITIES SECONDARY TO UNDERDIAGNOSIS AND RELIABILITY OF DIAGNOSTIC MARKERS IN DIFFERENT ETHNICITIES

Several scoring systems have been developed to detect hepatic fibrosis and progression of NAFLD, including alanine aminotransferase/aspartate aminotransferase (AST/ALT) ratio, NAFLD fibrosis score (NFS), Fibrosis-4 (FIB-4) index, and AST/platelet ratio index (APRI). De Silva et al.[21] noted that noninvasive markers, such as NFS, APRI, FIB-4, and AST/ALT ratio, were less sensitive at detecting advanced fibrosis in South Asian compared with white patients. In a study

involving a Chinese population, diagnostic value of miR-34a for NASH was superior to that of ALT, FIB-4, and APRI in the diagnosis of fibrosis in NASH.[22] Pan et al.[23] noticed that intermediate NFS and APRI scores were associated with hepatic steatosis in Hispanics, but FIB-4 scores were not as outlined in Fig. 2. As per Alazawi et al.,[24] a significant Bangladeshi population had elevated liver function tests, but 88.4% of patients did not have coded liver diagnosis, demonstrating significant underdiagnosis in that country.

GENETIC DISPARITIES

Several studies noticed genetic disparities in patients with NAFLD. An allele in Patatin-like phospholipase domain-containing protein 3 (PNPLA3) was found to be strongly associated with increased risk for NAFLD and was most commonly seen in Hispanics. In a study by Kallwitz et al.,[25] 9342 participants with NAFLD demonstrated PNPLA3 G frequency was different among Hispanics, with the highest proportion in Mexicans (52%) and the lowest in Dominicans (23%). Also, Hispanics with American ancestry had increased risk for NAFLD, whereas those with African and European ancestry were inversely associated with NAFLD.[25] As per Carrasco et al.,[26] lysophospholipase like 1 (LYPLAL1), Protein Phosphatase 1 Regulatory Subunit 3B (PPP1R3B), and Glucokinase Regulator (GCKR) are also associated with increased NAFLD in Mexicans. Membrane Bound O-Acyltransferase Domain Containing 7 (MBOAT7) plays an important role in development of NAFLD in Europeans by increasing hepatic fat accumulation.[27] A meta-analysis including 12 case-controlled studies showed that the single-nucleotide polymorphism (SNP) rs738409 G allele increases risk for NAFLD in Asian populations.[28] As summarized in Fig. 3, the earlier genetic variations are influenced by ethnicity and affect the susceptibility of different races to NAFLD.

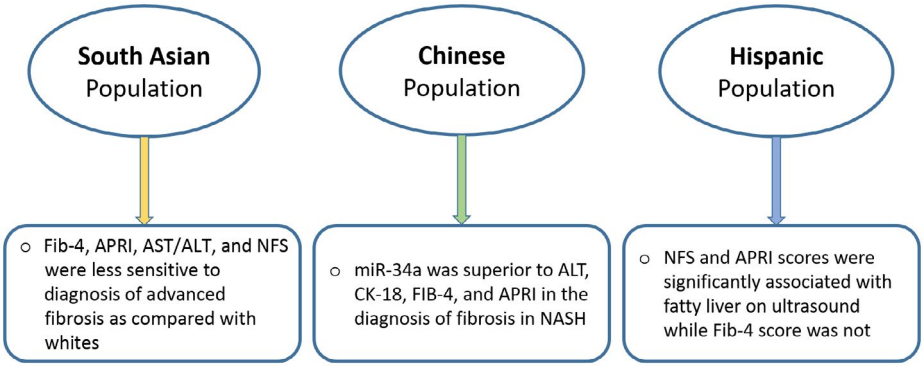

FIG 2 Disparities in the reliability of diagnostic markers among ethnicities.

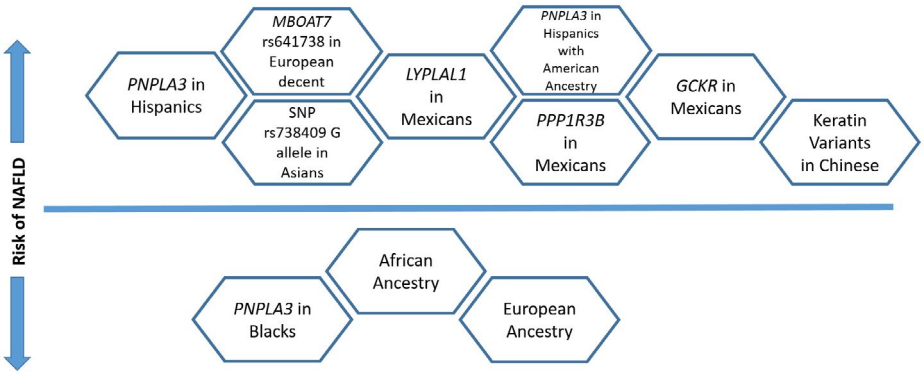

FIG 3 Genetic and racial influences on NAFLD risk. Factors above the horizontal line represent an increased risk for NALFD, whereas factors below the horizontal line reduce the risk for NALFD. Data are from Kallwitz et al.,[25] Larrieta-Carrasco et al.,[26] Li et al.,[51] Mancina et al.,[27] Zhang et al.,[28] and Romeo et al.[52]

DISPARITIES IN PROGNOSIS OF DIFFERENT ETHNICITIES

NASH-Related Cirrhosis and HCC in Different Races

A systematic review done in south Texas and another large, retrospective analysis of patients undergoing liver transplant showed Hispanics experienced greatest burden of NAFLD-related HCC compared with other ethnicities.[29,30] Non-US-born Hispanics are at lower risk for HCC compared with US-born Hispanics, whereas foreign-born Asians are at increased risk for HCC compared with US-born Asians.[31] Hispanic and white patients were likely to be diagnosed with cirrhosis at an age younger than 40 years compared with African American patients.[32]

Significance of Racial Disparities in Patients Undergoing Liver Transplantation

Couto et al.[33] noted that patients of Hispanic ethnicity are at increased risk for needing liver transplant for NASH-related HCC. As per the United Network for Organ Sharing database, African Americans had lower post–liver transplant survival compared with non-Hispanic whites.[34] Ha et al.[35] noticed that Caucasians are at increased risk for liver cirrhosis, but after 88 months of follow-up, Asians, Hispanics, and Caucasians are equally at increased risk for cirrhosis, HCC, hepatic decompensation, and all-cause mortality.

NASH-Related Morbidity and All-Cause Mortality in Different Ethnicities

As per NHANES III data published in 2008, NAFLD had higher overall mortality and liver-related mortality than the general US population.[36] Younossi and colleagues[37] reported significantly higher rates of all-cause mortality among blacks than whites in the NAFLD cohort. Yet another study showed there was no difference in all-cause mortality in different ethnicities. Patients with NAFLD are at increased risk for cardiovascular mortality and are closely associated with the presence of metabolic factors, which vary in different ethnicities.[38] NAFLD is strongly associated with increased stroke risk in white patients compared with black patients.[39] A recent meta-analysis included six studies and noted that racial disparities overall played a smaller role in NAFLD prognosis compared with prevalence.[5]

CONCLUSION

There are notable racial disparities in multiple aspects of NAFLD, including its prevalence, severity, genetic predisposition, and overall prognosis. NAFLD prevalence was lowest in African Americans and highest in Hispanics in the majority of studies. *PNPLA3* gene is strongly associated with NAFLD and mostly seen in Hispanics. Concerning prognosis, limited studies among various racial subsets in NAFLD do not always corroborate one another. In conclusion, studies are urgently needed to identify determinants of NAFLD disparities and design appropriate intervention strategies to reduce racial disparities to improve NAFLD-related morbidity and mortality.

CORRESPONDENCE

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