Clinical and Histologic Characterization of Nonalcoholic Steatohepatitis in African American Patients

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OBJECTIVE

There has been a widespread misconception among physicians that African Americans are protected from developing nonalcoholic steatohepatitis (NASH). However, a formal histologic and metabolic comparison against well-matched Caucasians has never been performed.

RESEARCH DESIGN AND METHODS

Sixty-seven African American patients were matched 2:1 to Caucasians (*n* = 134) for age, sex, BMI, hemoglobin A_{1c}, and prevalence of type 2 diabetes mellitus (T2DM). Screening for NASH included measurement of intrahepatic triglyceride content by proton MRS (^{1}H-MRS), followed by a liver biopsy if patients had hepatic steatosis. Insulin resistance was estimated during an oral glucose tolerance test using the Matsuda Index.

RESULTS

Compared with Caucasians, African American patients had a lower intrahepatic triglyceride content (mean ± SD 6.1 ± 6.8% vs. 9.4 ± 7.5%, *P* = 0.007) and the presence of nonalcoholic fatty liver disease (NAFLD) was less common (25.0% vs. 51.9%, *P* = 0.003). However, prevalence of NASH was not different between ethnicities in patients with NAFLD (57.1% vs. 73.3%, *P* = 0.12). Moreover, they showed similar severity in each of the individual histologic parameters (inflammation, ballooning, and fibrosis). Among patients with NAFLD, insulin resistance was similar between both ethnic groups (Matsuda Index: 3.3 ± 1.8 vs. 3.1 ± 1.9, *P* = 0.61; adipose tissue insulin resistance [Adipo-IR] index: 5.7 ± 4.6 vs. 6.4 ± 4.7 mmol/L · μU/mL, *P* = 0.53) but appeared to be worse in African American versus Caucasian patients without NAFLD (Matsuda Index: 4.9 ± 3.6 vs. 7.0 ± 4.9, *P* = 0.11; Adipo-IR: 3.9 ± 2.8 vs. 2.7 ± 2.3 mmol/L · μU/mL, *P* = 0.06). African American patients also had lower plasma triglycerides and higher HDL cholesterol, independent of the severity of intrahepatic triglyceride.

CONCLUSIONS

Although African Americans have lower intrahepatic triglyceride accumulation, once NAFLD develops, NASH occurs as frequently, and as severe, as in Caucasian patients. Therefore, African Americans with NAFLD should be screened for NASH with the same degree of clinical resolve as in Caucasian patients.

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Nonalcoholic fatty liver disease (NAFLD) is defined as the accumulation of more than 5% of visible steatosis within hepatocytes on light microscopy, or more than 5.56% of intrahepatic triglyceride content on imaging such as proton MRS (^{1}H-MRS) (1,2). Using liver ^{1}H-MRS, the Dallas Heart Study (DHS) found that more than one-third of participants had a diagnosis of NAFLD (3). Moreover, the study showed important differences among ethnicities, with African Americans having a significantly lower prevalence of NAFLD compared with Caucasians and Hispanics. Similar results were reported from the Third National Health and Nutrition Examination Survey (NHANES III) based on ultrasound findings (4).

Based on results from these studies, there has been a growing misconception among primary care providers that subjects of African American ancestry are protected against the more severe form of the disease, nonalcoholic steatohepatitis (NASH). This has resulted in NASH being dismissed and frequently overlooked in this population. Moreover, NASH in African American patients has been rarely studied by means of a liver biopsy, and the few available studies have been rather small (5,6). Therefore, the risk of developing NASH and fibrosis in African American patients with NAFLD has been neglected and remains unclear.

Among patients undergoing bariatric surgery, Solga et al. (6) reported that NASH was less common in African Americans than in Caucasians but still affected 27% of patients. Another report found slightly less frequent NASH in African Americans versus Caucasians among morbidly obese subjects but similar degrees of liver fibrosis (7). However, results from morbidly obese individuals may not represent the overall obese population. Fewer data exist about the frequency of NASH in patients who are only overweight or mild to moderately obese. In a study by Williams et al. (5), the prevalence of NASH among patients with NAFLD was actually higher among African Americans when compared with Caucasians. However, only a small group of African Americans underwent a percutaneous liver biopsy in this study (n = 13).

Given the limited and conflicting evidence, the aim of the current study was to determine the prevalence of NASH in a large cohort of African American patients, and their histologic and metabolic characteristics compared with well-matched Caucasian individuals.

RESEARCH DESIGN AND METHODS

Subjects

A group of 67 African American participants were recruited from hepatology and endocrinology clinics, as well as from the general population (newspaper ads and flyers) of Gainesville, FL, and San Antonio, TX, as previously reported (8). Patients were selected based on overall increased risk of NAFLD/NASH, based on the presence of obesity, metabolic syndrome, type 2 diabetes mellitus (T2DM), or elevated plasma aminotransferases. Participants were excluded if they had a history of significant alcohol use ($\geq$30 g/day for males and $\geq$20 g/day for females), type 1 diabetes mellitus, or any liver disease other than NASH (i.e., hepatitis B or C, autoimmune hepatitis, hemochromatosis, Wilson disease, or drug-induced hepatitis). They were also excluded if they had any evidence of clinically significant renal, pulmonary, or heart disease. Two Caucasian control subjects were selected for each African American participant based on matching age, sex, BMI, hemoglobin A_{1c} (HbA_{1c}), prevalence of T2DM, and recruitment strategy (clinics vs. general population). Thus, out of the 240 Caucasian patients recruited based on similar inclusion and exclusion criteria, 134 were selected by propensity match scoring (total cohort n = 201). The study was approved by both institutional review boards, and a written informed consent was obtained from each patient prior to their participation.

Study Design

Metabolic and imaging measurements included the following: *1*) routine blood and urine testing, including fasting plasma glucose, HbA_{1c}, lipid profile, plasma aminotransferases, fasting plasma insulin (FPI), and fasting free fatty acids (FFAs); *2*) total body fat by dual-energy X-ray absorptiometry (DXA); *3*) intrahepatic triglyceride content by ^{1}H-MRS; *4*) HOMA of insulin resistance and adipose tissue insulin resistance during the fasting state expressed as the adipose tissue insulin resistance (Adipo-IR) index (FFA $\times$ FPI); *5*) a 75-g oral glucose tolerance test to establish the diagnosis of normal glucose tolerance or T2DM according to current criteria and to measure insulin resistance by the Matsuda Index; and *6*) liver biopsy to establish the diagnosis of NASH and the stage and grade of the disease.

Measurements of Total Body and Liver Fat Content

Total body fat content was measured by DXA (Hologic Inc., Waltham, MA). For the measurement of hepatic fat content, localized ^{1}H-NMR spectra of the liver were acquired as previously described (9). Two or three liver areas with a volume of 30 $\times$ 30 $\times$ 30 mm were selected for voxel placement. A liver fat content $>$5.56% was considered diagnostic of NAFLD.

Liver Biopsy

An ultrasound-guided liver biopsy was performed in patients with a diagnosis of NAFLD by ^{1}H-MRS. Histologic characteristics for the diagnosis of NASH were determined using standard criteria (10).

Statistical Analysis

Data were summarized in percentages for categorical variables and as mean $\pm$ SD for numeric variables. Categorical variables were compared performing χ^2 or Fisher exact test. For comparisons between two groups, we performed a Kruskal-Wallis or Student t test for numeric variables, depending on variable distribution. Pearson or Spearman correlations were used for numerical variables according to their characteristics. A two-way ANOVA was used to assess the role of the presence of T2DM in the ethnic differences observed between groups. A two-tailed value of $P < 0.05$ was considered to indicate statistical significance. Analyses were performed with Stata 11.1 (StataCorp LP).

RESULTS

Clinical and Metabolic Characteristics

Demographic, anthropometric, and clinical characteristics of the 201 patients included in the study can be observed in Table 1. They were well matched for age, sex, BMI, and prevalence of T2DM, as expected based on selection criteria for the control subjects. No significant differences were observed in fasting plasma glucose, FPI, or their use of medications for T2DM (metformin, sulfonylureas, and/or insulin) or statins.

Despite similar BMIs between ethnic groups, we observed lower total body fat among African Americans when compared with Caucasians. In addition, African Americans had lower plasma triglycerides and higher HDL cholesterol (HDL-C). In accordance with this,

Table 1—Demographic, anthropometric, and clinical characteristics of patients based on their ethnicity

	Caucasian patients (n = 134)	African American patients (n = 67)	P value
Age (years)	54 ± 10	54 ± 9	0.72
Sex (male) (%)	71	70	0.85
BMI (kg/m^2)	33.9 ± 5.1	34.5 ± 5.2	0.43
Total body fat (%)	36 ± 7	33 ± 8	0.004
Diagnosis of NAFLD (%)	52	25	0.003
T2DM (%)	70	73	0.66
Duration of T2DM (years)	6.3 ± 5.7	5.3 ± 5.2	0.41
Fasting plasma glucose (mg/dL)	139 ± 48	127 ± 39	0.09
FPI (μIU/mL)	12 ± 10	12 ± 8	0.86
HbA_{1c} (in T2DM) (%)	7.1 ± 1.3	7.0 ± 1.0	0.81
Use of metformin (%)	57	52	0.57
Use of sulfonylureas (%)	27	24	0.66
Use of insulin (%)	12	20	0.20
Cholesterol (mg/dL)	176 ± 46	169 ± 37	0.34
Triglycerides (mg/dL)	144 (97–210)	97 (71–140)	<0.001
HDL-C (mg/dL)	39 ± 10	46 ± 16	<0.001
LDL-C (mg/dL)	101 ± 38	102 ± 31	0.94
Use of statins (%)	68	60	0.31
ALT (IU/L)	43 ± 33	37 ± 34	0.21
AST (IU/L)	31 ± 18	31 ± 26	0.98

Data are presented as mean ± SD or median (interquartile range) for the numeric variables and as percentage for the categorical variables. ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDL-C, LDL cholesterol.

patients of African American ethnicity showed a significantly lower intrahepatic triglyceride accumulation compared with Caucasians ([mean ± SD] 6.1 ± 6.8% vs. 9.4 ± 7.5%, P = 0.007). This resulted in a lower proportion of patients with NAFLD among African Americans when compared with Caucasians (25.0% vs. 51.9%, P = 0.003). Of note, ethnic differences in intrahepatic triglyceride accumulation were only statistically significant among patients with elevated total body fat (defined as total body fat above the median [35.4%]; intrahepatic triglyceride content difference in this subgroup: 5.8%, P = 0.015). No differences were observed in plasma alanine aminotransferase (43 ± 33 vs. 37 ± 34 IU/L, P = 0.21) or plasma aspartate aminotransferase (31 ± 18 vs. 31 ± 26 IU/L, P = 0.98) between ethnicities.

When patients were divided based on the presence or absence of NAFLD (Fig. 1), we observed that intrahepatic triglyceride accumulation was similar between Caucasians and African Americans with NAFLD. In other words, once patients develop NAFLD, they accumulate the same amount of intrahepatic triglycerides regardless of their ethnicity. Despite this similar intrahepatic triglyceride content, we still observed lower plasma triglyceride and higher plasma HDL-C levels among African Americans compared with Caucasians regardless of presence/absence of NAFLD (Fig. 1*B* and *C*).

Despite differences in the proportion of patients with NAFLD, no significant differences were observed in insulin resistance between ethnicities when measured in the fasting or postprandial state (Supplementary Fig. 1). Moreover, when subjects were divided based on the presence or absence of NAFLD, we observed that both ethnicities were equally insulin resistant once NAFLD developed (Fig. 2). However, in patients without NAFLD, there was a strong trend toward worse insulin resistance among African Americans, especially when measured as Matsuda Index (4.9 ± 3.6 vs. 7.0 ± 4.9, P = 0.11) and Adipo-IR (3.9 ± 2.8 vs. 2.7 ± 2.3 mmol/L · μU/mL, P = 0.06). This occurred in spite of similar intrahepatic triglyceride content.

Histologic Characteristics

Overall, the presence of NASH among the entire cohort of patients was significantly lower for African American patients compared with Caucasians (22.2% vs. 48.2%, P = 0.001), likely due to the lower frequency of patients with NAFLD in the cohort. However, when only patients with a diagnosis of NAFLD by ^{1}H-MRS were considered, we observed that as many as 57.1% of African American patients with NAFLD had NASH in their liver biopsy. Moreover, there was not a significant difference in the prevalence of NASH between African Americans and Caucasians with NAFLD (57.1% vs. 73.3%, P = 0.12). To further analyze the severity of liver disease in the two ethnic groups, liver histology from patients with NASH was compared between African American and Caucasian patients. As can be observed in Fig. 3, there were no significant differences in any of the histologic parameters between the two ethnic groups.

Subgroup Analysis

Both ethnic groups were matched for prevalence of T2DM and HbA_{1c}, but in order to further assess the role of hyperglycemia in ethnic differences, we repeated all the above analyses separating patients with and without T2DM. This information can be found in Supplementary Table 1. As can be observed, no significant differences were observed compared with the overall cohort. Moreover, ethnic differences in the prevalence of NAFLD (P = 0.017), plasma triglycerides ($P <$ 0.001), plasma HDL-C ($P <$ 0.001), and total body fat by DXA (P = 0.001) remained statistically significant even after adjusting for the presence of T2DM.

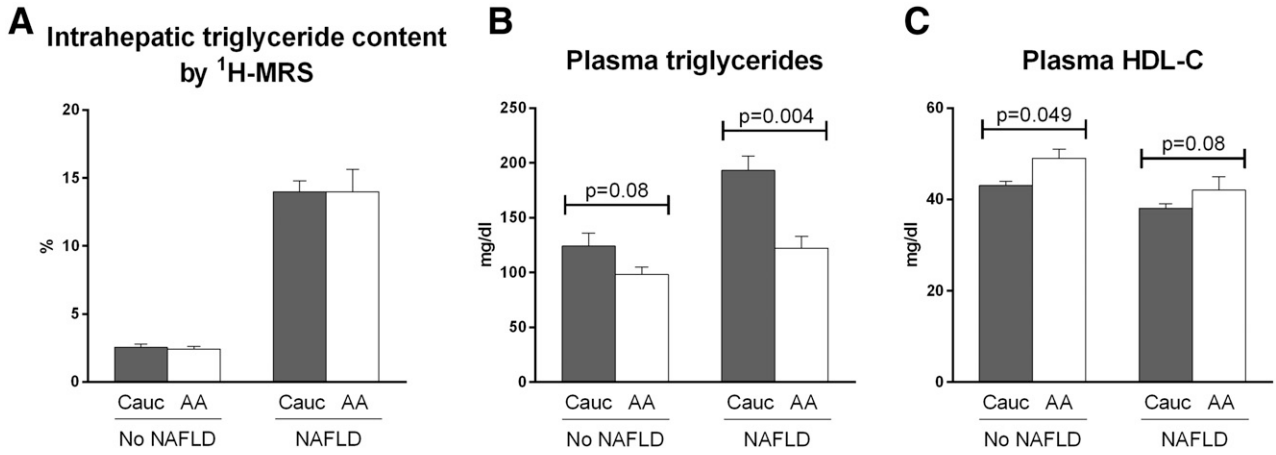

Figure 1—Intrahepatic triglyceride content (*A*), plasma triglycerides (*B*), and plasma HDL-C (*C*) in Caucasian (Cauc) and African American (AA) patients based on the presence/absence of NAFLD. Data are presented as mean ± SEM. Only *P* values <0.15 are represented.

Other sensitivity analyses can also be found in Supplementary Table 1.

CONCLUSIONS

There is a common belief among primary care physicians, hepatologists, and endocrinologists that African Americans are protected from developing NASH. As a consequence, they are frequently underdiagnosed in the clinical setting and underrepresented in clinical trials for NASH. This misperception about African Americans probably arises from epidemiologic studies showing a lower prevalence of NAFLD in this ethnic group (3,4). In the absence of follow-up liver biopsy studies examining the prevalence of NASH, the assumption has been that they are at a lower risk. Our results are important because they show that the current neglect in screening African American patients for NASH is not justified. Although they may develop hepatic steatosis less often, once they do so, their risk of NASH is similar to that of Caucasians. The clinical implication of this is that African Americans with NAFLD should be carefully evaluated for NASH with as much determination as Caucasian patients.

The issue on the prevalence of NAFLD across ethnicities has been controversial. Current dogma, based largely on the DHS (3), states that Hispanics have a greater risk than Caucasians, and African Americans the least among the three groups. However, this large epidemiologic study did not differentiate hepatic steatosis from other secondary causes (i.e., alcohol intake) and other factors such as sex (i.e., African American women had similar rates of steatosis compared with Caucasian females) or presence of obesity or T2DM (higher in Hispanics and African Americans). We have previously highlighted the importance of controlling for clinical variables by reporting that, in contrast to current belief, when Caucasians and Hispanics were well matched for BMI and insulin resistance, there were no differences in the severity of hepatic steatosis by ^{1}H-MRS or in the severity of liver histology in patients with NASH (11). In the current study, we report that despite having an overall lower intrahepatic triglyceride content, African Americans with NAFLD had a similar prevalence of NASH compared with well-matched Caucasian patients. This is in line with prior reports; in a large study by Bambha et al. (12), prevalence of NASH was only slightly lower in African Americans (52% vs. 62% in non-Hispanic whites), but African Americans represented only 5% of the

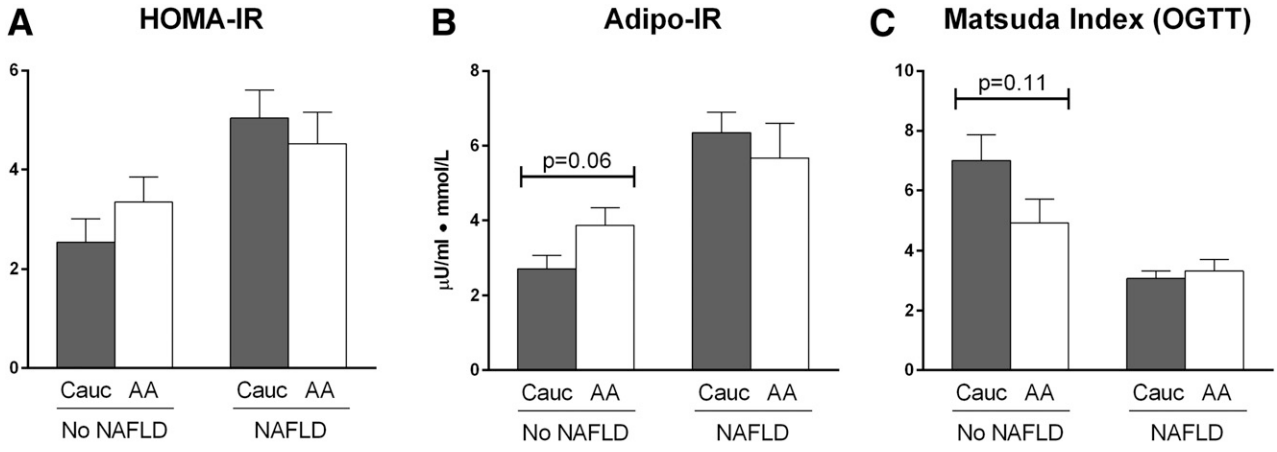

Figure 2—Insulin resistance expressed as HOMA of insulin resistance (HOMA-IR) (*A*), Adipo-IR (*B*), and Matsuda Index (*C*) in Caucasian (Cauc) and African American (AA) patients based on the presence/absence of NAFLD. Data are presented as mean ± SEM. Only *P* values <0.15 are represented. OGTT, oral glucose tolerance test.

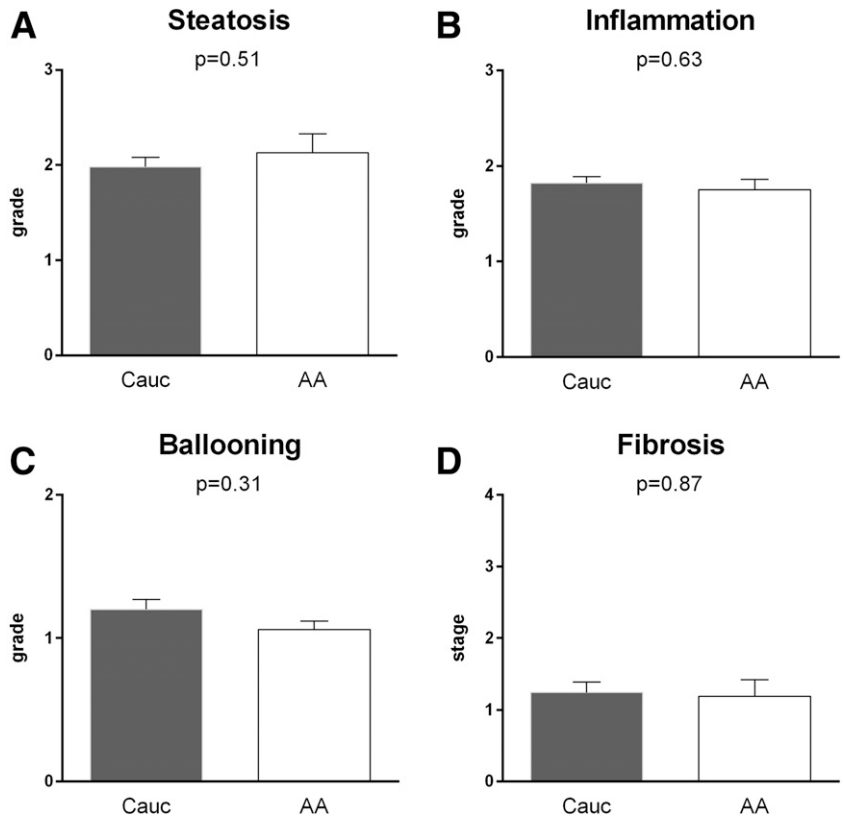

Figure 3—Histologic severity of steatosis (*A*), inflammation (*B*), ballooning (*C*), and fibrosis (*D*) among patients with NASH based on ethnicity. Data are presented as mean ± SEM. AA, African American; Cauc, Caucasian.

entire cohort and just 27 had a liver biopsy. In addition, recent data from the Multiethnic Cohort study (13), including 5,783 patients with chronic liver disease, showed that although the prevalence of NAFLD was lowest in African Americans, it was still the second most common cause of cirrhosis in this ethnic group.

Moreover, the prevalence of NASH among patients with NAFLD was not the only similarity between Caucasians and African Americans; both ethnic groups showed similar severity of all histologic parameters, including fibrosis. These findings imply that the mechanisms responsible for the progression from isolated steatosis to NASH may be similar in African American and Caucasian patients. On the contrary, intrahepatic triglyceride deposition was significantly different between ethnic groups. As we have previously demonstrated, insulin resistance at the level of the adipose tissue is a major driver of intrahepatic triglyceride accumulation (8,14). In accordance with this, Adipo-IR was equally correlated with intrahepatic triglyceride content in both Caucasians and African Americans (r = 0.46, $P < 0.001$ and$r$ = 0.38, P = 0.006, respectively). However, for any level of Adipo-IR, African American patients showed a lower intrahepatic triglyceride content. Our interpretation of these results is that although African Americans and Caucasians may have similar plasma FFA levels reaching the liver, African American patients are able to better compensate for FFA overload by probably increasing β-oxidation. We speculate that Caucasians, on the other hand, may be more prone to triglyceride accumulation (i.e., more steatosis) and try to compensate by increased VLDL secretion (i.e., higher plasma triglyceride levels when compared with African Americans). Future studies assessing hepatic mitochondrial function and lipid turnover will be needed to fully understand these differences.

In the current work, insulin resistance measured in the fasting or postprandial states was similar between both ethnic groups when all patients (patients with or without NAFLD) were included in the analysis. Prior studies assessing insulin resistance in African Americans and Caucasians have shown conflicting results, with some studies suggesting worse (15–17) versus similar (18,19) insulin resistance among African Americans. These discrepancies could potentially be explained by different clinical characteristics of the patients studied or differences in dietary composition or physical activity, which were not assessed in the current study. When the focus has been on patients with obesity and/or T2DM (i.e., insulin-resistant patients), there has been no difference between ethnic groups (18), whereas those studies including relatively healthy individuals (i.e., more insulin-sensitive patients) observed worse insulin resistance among African Americans when compared with Caucasians (15). In accordance with these prior findings, we also observed that among patients with a diagnosis of NAFLD (i.e., insulin-resistant patients), both ethnic groups showed similar insulin resistance. However, worse insulin resistance was present in African American compared with Caucasian patients among those without a diagnosis of NAFLD (i.e., more insulin-sensitive patients) (Fig. 2). Similarly, in the study by Healy et al. (20), modestly severe obesity attenuated the ethnic differences in insulin sensitivity. Of note, when African American and Caucasian patients were matched for adiposity, insulin sensitivity was also similar between ethnic groups (19). This is important as insulin sensitivity appears to be associated with worse liver histology in NASH, although the mechanisms of this association are unclear (21).

In accordance with prior reports (15,22), we have found that African Americans have lower plasma triglycerides and higher plasma HDL-C when compared with Caucasians. We have recently published that this dyslipidemic profile, characterized by hypertriglyceridemia, low HDL-C, high number of apolipoprotein B (apoB) particles, and small LDL size, is typical of insulin-resistant states and NAFLD, but it is not affected by the presence or the severity of NASH (23). Results from the current work have expanded on the important role of ethnicity as a determinant of the dyslipidemic profile irrespective of insulin resistance or hepatic steatosis. When divided by presence or absence of NAFLD, African American patients showed lower triglyceride levels and higher HDL-C despite similar insulin resistance and intrahepatic triglyceride

accumulation. This suggests that other mechanisms may account for this more benign dyslipidemic profile among African Americans. For instance, genetic variations affecting lipoprotein metabolism may explain, at least in part, differences observed between ethnic groups (24). For example, single nucleotide polymorphisms in human hepatic lipase or lipoprotein lipase have been described with higher frequency among African American subjects (25,26). Genetic variations of apoCI, apoCIII, and apoE have also been reported in African American subjects with different frequencies than in Caucasian subjects (27,28). Also, previous studies have found that paraoxonase-1 (PON1) is lower in African Americans compared with Caucasians, suggesting potential HDL-C dysfunction in this ethnic group (20).

In summary, we have shown in the current work that although African Americans have a lower accumulation of intrahepatic triglycerides, once they develop NAFLD, NASH develops as frequently and with similar severity as observed in Caucasian patients. Moreover, we observed that insulin resistance was similar among ethnic groups, and therefore it does not explain the differences in intrahepatic triglyceride content observed between African Americans and Caucasians. These findings are important because they call for a paradigm shift in our current clinical practice: African American patients with NAFLD should be screened for NASH with the same degree of suspicion as in Caucasians. Larger, prospective studies are much needed to confirm these findings.

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Author Contributions. F.B. recruited and followed up with patients; acquired, analyzed, and interpreted data; performed statistical analysis; and wrote, edited, and reviewed the manuscript. P.P.-S. recruited and followed up with patients and acquired data. I-C.L. analyzed and interpreted data and wrote, edited, and reviewed the manuscript. S.K. and K.D. acquired data and revised the manuscript. K.C. recruited and followed up with patients; acquired, analyzed, and interpreted data; critically revised the manuscript; and obtained funding. F.B. and K.C. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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