Nonalcoholic Fatty Liver Disease in Nonobese Subjects of African Origin Has Atypical Metabolic Characteristics

Debbie S. Thompson,[1] Ingrid A. Tennant,[1,2] Deanne P. Soares,[2] Clive Osmond,[3] Chris D. Byrne,[4,5] Terrence E. Forrester,[1] and Michael S. Boyne[1,6]

[1]Caribbean Institute for Health Research, The University of the West Indies, Kingston 7, Jamaica; [2]Department of, Surgery, Radiology, Anesthesia and Intensive Care, The University of the West Indies, Kingston, Jamaica; [3]MRC Lifecourse Epidemiology Unit, University of Southampton, Southampton, SO16 6YD United Kingdom; [4]Nutrition and Metabolism, Faculty of Medicine, University of Southampton, Southampton, SO16 6YD United Kingdom; [5]Southampton National Institute for Health Research Biomedical Research Centre, University Hospital Southampton, Southampton General Hospital, Southampton, SO16 6YD United Kingdom; and [6]Department of Medicine, The University of the West Indies, Kingston 7, Jamaica

ORCiD numbers: 0000-0001-6781-7646 (D. S. Thompson); 0000-0002-6458-8240 (D. P. Soares); 0000-0002-9054-4655 (C. Osmond); 0000-0002-9602-8694 (C. D. Byrne); 0000-0001-7976-8669 (T. E. Forrester); 0000-0003-4560-9285 (M. S. Boyne).

Background: Nonobese nonalcoholic fatty liver disease is reported in several populations. However, because persons of African origin display unique fat accumulation, insulin resistance, and lipid profiles, we investigated fatty liver in nonobese persons of African origin.

Method: We recruited 78 urban Jamaican volunteers. CT was used to estimate liver and abdominal fat and dual-energy X-ray absorptiometry to measure body composition. Fasting blood was collected for lipids, alanine aminotransferase (ALT), adiponectin, and fetuin-A. Homeostatic model assessment of insulin resistance (HOMA-IR), whole-body insulin sensitivity index (WBISI), insulinogenic index (IGI), and oral disposition index (oDI) were calculated after a 75-g oral glucose tolerance test.

Results: Fifty-two percent of participants were male; mean (±SD) age was 28.5 ± 7.8 years, and body mass index was 22.4 ± 3.0 kg/m^2. Mean liver attenuation (MLA) and liver/spleen (LS) ratio, both inversely correlated to liver fat, were 62.8 ± 4.3 HU and 1.2 ± 0.1, respectively; 3.8% of participants had liver fat >30% (LS ratio < 1). In age, sex, and BMI-adjusted correlations, MLA was negatively associated with weight ($r = -0.30$; $P = 0.009$) and height ($r = -0.28$; $P = 0.017$) and was associated with fasting glucose ($r = 0.23$; $P = 0.05$), fasting insulin ($r = 0.42$; $P \leq 0.001$) and HOMA-IR ($r = 0.35$; $P = 0.004$). Serum lipids, ALT, adiponectin, fetuin-A, WBISI, IGI, and oDI were not associated with liver fat.

Conclusions: In nonobese Afro-Caribbean participants, greater liver fat was associated with weight and height and lower fasting insulin and hyperinsulinemia appears to be influential in the reduction of NAFLD. These findings may be influenced by ethnicity, body size, and method of estimating liver fat.

Abbreviations: ALT, alanine aminotransferase; BMI, body mass index; CV, coefficient of variation; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment of insulin resistance; IGI, insulinogenic index; LDL-C, low-density lipoprotein cholesterol; LS, liver/spleen; LS ratio, ratio of mean liver/spleen attenuation; MLA, mean liver attenuation; NAFLD, nonalcoholic fatty liver disease; oDI, oral disposition index; OGTT, oral glucose tolerance test; SAT, subcutaneous adipose tissue; TG, triglyceride; VAT, visceral adipose tissue; WBISI, whole-body insulin sensitivity index.

Received 8 April 2019
Accepted 15 August 2019
First Published Online 21 August 2019

ISSN 2472-1972
November 2019 | Vol. 3, Iss. 11
doi: 10.1210/js.2019-00138 | Journal of the Endocrine Society | 2051–2063

Freeform/Key Words: nonobese nonalcoholic fatty liver disease, insulin resistance, adiponectin, fetuin-A

Nonalcoholic fatty liver disease (NAFLD) is the most prevalent liver disease in Western countries [1], and it is rapidly becoming the most common liver disease worldwide [2]. It is also a major public health concern because of its association with cardiovascular risk factors [3]. NAFLD occurs when an imbalance between triglyceride accumulation and removal in hepatocytes results in fat accumulation >5% of liver weight without substantial alcohol intake. Although most commonly diagnosed in persons with obesity, NAFLD also occurs in lean/nonobese individuals. Nonobese NAFLD is defined as fatty liver with a body mass index (BMI) <25 kg/m^2 in Asians and <30 kg/m^2 in people of other races [4]. Its reported global prevalence ranges from 3% to ~30% [5], and the prevalence in Western populations is 7% to 21% [6–8].

Nonobese NAFLD is not well understood, and reports regarding its clinical and metabolic features are inconsistent. The third National Health and Nutrition Examination Survey (NHANES III) reported that compared with an overweight-obese NAFLD group, the lean NAFLD cohort was younger and more commonly female, with significantly lower prevalence of IR, DM, hypercholesterolemia, and hypertension [8]. Similarly, in a meta-analysis of 16 studies involving various ethnic groups, lean and obese patients with NAFLD shared altered metabolic and cardiovascular profiles with the effects in lean patients having lesser magnitude [9]. In contrast, patients from Korea with nonobese NAFLD had significantly higher prevalence rates of elevated blood pressure, impaired fasting glucose, low high-density lipoprotein cholesterol (HDL-C), and high triglyceride (TG) concentrations than patients with obesity and NAFLD, especially among women [10].

The role of ethnicity in these conflicting findings is unknown; in addition, very little is known about nonobese NAFLD in persons of African origin. The prevalence of nonobese NAFLD (BMI < 30 kg/m^2) has been reported to be 18% among Hispanic Americans, 9% among whites, and 6% among African Americans [7]. In addition, several metabolic variables commonly associated with fatty liver disease may not reliably predict liver fat in persons of African origin. Low-density lipoprotein cholesterol (LDL-C) and TG levels are associated with liver fat [11]; however, persons of African origin have normal TG and low HDL-C levels as the characteristic lipid profile of insulin resistance (*i.e.,* the so-called *triglyceride paradox*) [12]. Notable also is the fact that blacks have a lower prevalence of fatty liver than Hispanics with similar levels of obesity and insulin resistance [6]. This distinct metabolic response to insulin resistance reported in African Americans (*i.e.,* the insulin resistance paradox) [13] may also be a feature of nonobese NAFLD. Finally, visceral obesity reportedly plays an important role in the pathogenesis of lean NAFLD [14]. However, African Americans may be less likely to accumulate visceral adipose tissue (VAT) than Asians and whites [15].

These findings suggest that distinct mechanisms may underlie the pathogenesis of NAFLD in persons of African origin. This study aimed to investigate the clinical and biochemical parameters associated with liver fat in nonobese Jamaican adults using an objective measure of both hepatic and visceral fat. A secondary aim was to identify predictors of liver fat in this study population. We hypothesized that fatty liver in nonobese persons of African origin is not associated with insulin resistance or lipid level.

1. Methods

A. Subjects

We identified 84 individuals from urban Jamaican communities who were previously recruited by community health aides as healthy community controls in a larger study involving Jamaican adults [16]. Each participant was recruited as follows: Beginning at a specified address, visits were conducted house to house alternately on either side of the road.

Failure to find a participant resulted in adjacent streets being visited in a similar manner. Potential recruits were asked about their general health status using a questionnaire, and height and weight measurements were conducted in the field using a stadiometer and a digital scale that was calibrated daily [16]. Individuals with a BMI <30 kg/m^2 were defined as nonobese. Exclusion criteria were a known history of liver disease, use of medications that cause liver abnormalities, and self-reported alcohol intake of >14 drinks per week for men and >7 drinks per week for women [17]. The Faculty of Medical Sciences/University Hospital of the West Indies Ethics Committee approved the study protocol (ECP 17, 14/15), and each participant gave written informed consent.

B. Measurements

After a 10-hour overnight fast, participants reported to the metabolic clinic at the Tropical Metabolism Research Unit and completed a staff-administered questionnaire. Body weight was measured to the nearest 0.1 kg and height and waist circumference to the nearest 0.1 cm using a standardized protocol [18]. A whole-body DEXA scan was performed on each participant to measure body composition (Lunar Prodigy; GE Healthcare, Madison, WI). Ten milliliters of fasting blood was collected for total cholesterol, HDL-C, LDL-C, triglycerides, alanine aminotransferase (ALT), adiponectin, and fetuin-A assays. A 75-g oral glucose tolerance test (OGTT) was conducted and 5-mL samples taken at 0, 30, 60, 90, and 120 minutes in fluoridated and heparinized chilled tubes for plasma glucose and insulin measurements, respectively.

Abdominal CT scans (Philips Brilliance 64-slice scanner, Willowick, OH) were conducted to measure hepatic steatosis and visceral adiposity. A single cross-sectional 5-mm-wide CT scan (120 kVp, 100 mA) was taken at the mid-intervertebral disc space between T12 and L1 to include images of both the liver and spleen; a second scan was obtained at the middle of the L4/L5 disc space to measure total and subcutaneous adiposity. During the scans, the machine was operated in tissue optimization mode.

C. Assays

Glucose concentration was determined by using the glucose oxidase method on an autoanalyzer. Insulin concentration was measured with an ELISA assay (ALPCO Diagnostics, Salem, NH) [19], which had analytical sensitivity of 0·399 μIU/mL and an intra-assay coefficient of variation (CV) $<5\%$ in our laboratory. Total cholesterol, HDL-C, TGs, and ALT were measured by enzymatic techniques using a COBAS INTEGRA 400 Plus Analyzer (Roche Diagnostics, IN). LDL-C was calculated by using the Friedewald formula [20]. Adiponectin was measured using a commercial ELISA kit (EMD Millipore Corporation, MA) [21]; the minimum detectable concentration was 0.78 ng/mL. The intra-assay CV was $<7.4\%$, and the interassay CV was $<8.4\%$. Fetuin-A was estimated by an ELISA method (ALPCO Diagnostics) [22]. The analytical sensitivity of the human fetuin-A ELISA was 5.0 ng/mL, and the interassay and intra-assay CVs were $\leq 6.8\%$.

D. Data Analysis

Liver fat data were analyzed using eFilm software (Merge Healthcare, Hartland, WI). Three regions of interest were placed in the image of the liver and one in the image of the spleen, each measuring a minimum of 1 cm^2. Tissue attenuation was measured in Hounsfield units (HU). The ratio of mean liver/spleen attenuation (LS ratio) was calculated, and a ratio of ≤ 1 or a mean liver attenuation (MLA) of ≤ 40 HU was used to indicate major hepatic steatosis ($>30\%$) [17]. CT scans have a reported sensitivity of 82% to 93% and a specificity of 100% for steatosis $>30\%$ [23].

Total and intra-abdominal fat area and mass were measured using the commercial software package QCT Pro, Tissue Composition Module Beta 1.0 (Mindways, Austin, TX). CT images were transferred to the Tissue Composition Module Beta 1.0 software package for analysis. The QCT Pro tissue analysis report provided composition results for total

abdominal adiposity and VAT in terms of mass (grams), area (centimeters squared), and volume (centimeters cubed) [24]. Subcutaneous adipose tissue (SAT) was calculated by subtracting VAT from total abdominal adiposity.

E. Calculations

The following formulae were used in the analyses:

1. Homeostatic model assessment-insulin resistance (HOMA-IR) = $I_0 \times G_0/22.5$, where G_0 and I_0 reflect basal (fasting) glucose and insulin in SI units [25].
2. Whole-body insulin sensitivity index (WBISI) = $10{,}000/(G_0 \times I_0 \times G_m \times I_m)^{0.5}$, where G_0 and I_0 reflect basal glucose and insulin and G_m and I_m reflect the mean concentrations of glucose and insulin during an OGTT.
3. Insulin secretion was estimated using the insulinogenic index (IGI) = $(I_{30} - I_0)/(G_{30} - G_0)$, where I_{30} and I_0 are insulin concentrations at 30 and 0 minutes and G_{30} and G_0 are glucose concentrations at 30 and 0 minutes.
4. Oral disposition index (oDI); β-cell function adjusted for insulin sensitivity = IGI × WBISI. oDI is a biomarker for predicting the development of type 2 diabetes mellitus.

F. Statistical Analysis

On the basis of a reported 11% prevalence of nonobese NAFLD in African Americans (by CT) [7], the sample size to achieve a precision of 7% and 80% power was 69. Continuous variables were expressed as means ± SDs when data were normally distributed and as medians (quartiles) when data were not normally distributed. Characteristics of men and women were compared using the independent *t* test. Variables that were not normally distributed were log-transformed to a normal distribution. Using LS ratio and MLA as continuous outcome variables, partial correlations were conducted with age, sex, and BMI as control variables. An informal forward variable selection approach was used to identify predictors of fatty liver using a P value <0.05 as the criterion for inclusion. Thirteen independent variables were identified *a priori* for this analysis: age, sex, height, weight, BMI, waist circumference, total cholesterol, LDL-C, TG, fasting glucose, fasting insulin, ALT, and the presence of type 2 diabetes mellitus. These variables were selected because of their documented associations with fatty liver disease as well as their routine use in clinical practice. SPSS 19.0 for Windows was used for the statistical analyses. Two-sided P values were reported, and a P value ≤ 0.05 was considered statistically significant.

2. Results

Eighty-four participants were recruited, of whom 81 consented to undergo abdominal CT. Three additional participants were excluded from the analysis because of insufficient CT data. Of the remaining 78 participants, 56% were male; mean ± SD age was 28.5 ± 7.8 years, and BMI was 22.4 ± 3.0 kg/m^2. Liver attenuation was 62.8 ± 4.3 HU, with a minimum of 53.4 HU and a maximum of 73.5 HU. Mean LS ratio was 1.2 ± 0.1, and the range was 0.95 to 1.78. Liver fat >30% was detected in 3.8% of participants on the basis of LS ratio ≤1. However, when the mean liver attenuation cutoff of ≤40 HU was used, no participants met the diagnostic criteria for moderate to severe fatty liver disease. Approximately 9% of participants had impaired glucose tolerance (*i.e.,* blood glucose level ≥7.8 mmol/L but <11.1 mmol/L after a 2-hour OGTT) [26].

Men weighed more, were taller, and had greater lean mass and greater ratio of visceral/subcutaneous fatty tissue (VAT/SAT), whereas women had greater fat mass, VAT, and SAT. Men had greater concentrations of fasting glucose, TGs, and ALT and had a higher oDI, whereas women had higher concentrations of fasting insulin, total cholesterol, and LDL-C

Table 1. Age, Anthropometry, Body Composition, Biochemical Characteristics, Glucose Metabolism, and Liver Fat of 78 Nonobese Urban Afro-Caribbean Participants

Clinical Variables	All Participants (N = 78)	Men (N = 44)	Women (N = 34)	*P* Value M vs W
Age, y	28.5 ± 7.8	29.1 ± 8.2	27.8 ± 7.2	0.46
Weight, kg	65.0 ± 10.7	69.1 ± 10.4	59.8 ± 8.7	<0.001
Height, cm	170.0 ± 10.1	176.4 ± 7.7	161.7 ± 6.0	<0.001
BMI, kg/m^2	22.4 ± 3.0	22.1 ± 2.5	22.9 ± 3.5	0.28
Fat mass, kg	9.9 (4.8, 20.0)	5.4 (3.8, 10.5)	20.6 (11.7, 25.4)	<0.001
Lean mass, kg	50.2 (38.1, 59.0)	58.7 (53.0, 63.4)	37.5 (35, 40.6)	<0.001
VAT area, cm^2	31.4 (16.2, 51.4)	24.3 (15.2, 39.5)	43.9 (25.7, 53.9)	0.035
SAT area, cm^2	75.1 (21.63, 165.7)	37.6 (5.4, 90.2)	154.9 (81.3, 222.3)	<0.001
VAT/SAT	0.5 (0.3, 0.8)	0.6 (0.5, 1.8)	0.3 (0.2, 0.4)	0.02
LS ratio	1.2 (1.1, 1.3)	1.2 (1.1, 1.2)	1.2 (1.1,1.3)	0.28
Mean liver attenuation, HU	62.8 ± 4.3	63.4 ± 4.6	62.2 ± 3.8	0.22
Total-C, mmol/L	4.0 ± 0.8	3.8 ± 0.7	4.3 ± 0.9	0.008
HDL-C, mmol/L	1.1 ± 0.3	1.1 ± 0.3	1.2 ± 0.3	0.54
LDL-C, mmol/L	2.6 ± 0.9	2.3 ± 0.8	2.9 ± 0.8	0.007
Triglycerides, mmol/L	0.7 (0.5, 0.8)	0.7 (0.6, 0.9)	0.6 (0.5, 0.8)	0.02
ALT, IU/L	8.0 (6.0,10.0)	8.0 (7.0, 11.0)	7.0 (5.0, 8.0)	0.01
Adiponectin, μg/mL	9.1 (6.9, 16.6)	8.1 (6.2, 12.3)	9.9 (8.9, 13.6)	0.08
Fetuin-A, g/L	0.5 ± 0.1	0.5 ± 0.1	0.5 ± 0.1	0.51
Fasting glucose, mmol/L	4.5 ± 0.5	4.7 ± 0.4	4.4 ± 0.6	0.005
2-h glucose, mmol/L	5.8 (4.9, 7.0)	5.8 (4.8, 6.5)	6.2 (4.9, 7.0)	0.2
Fasting insulin, μIU/mL	2.9 (1.5, 6.6)	2.0 (0.7, 3.5)	5.1 (2.7, 9.0)	0.006
HOMA-IR	0.6 (0.3, 1.3)	0.5 (0.2, 0.8)	1.0 (0.5, 1.8)	0.03
WBISI	161 (97, 245)	237 (156, 395)	109 (72, 160)	≤0.001
IGI	2.2 ± 0.9	2.4 ± 1.1	2.0 ± 0.4	0.08
oDI	304 (179, 685)	463 (229, 878)	221 (136, 337)	0.003

Variables are expressed as mean ± SD when data were normally distributed and median (first quartile, third quartile) when data were not normally distributed.
Abbreviations: Total-C, total cholesterol; M, men; W, women.

and were more insulin resistant (HOMA-IR and WBISI) than men. Despite this, men and women had similar amounts of liver fat (Table 1).

A. Anthropometry, Body Composition, and Liver Fat

After adjustments for age, sex, and BMI, MLA had a negative association with adult body weight ($P = 0.009$), height ($P = 0.017$), and lean mass ($P = 0.003$). The association between lean mass and MLA remained after further adjustment for fat mass ($r = -0.27$; $P = 0.02$) but was lost after adjustment for height ($r = -0.11$; $P = 0.35$) (data not shown). Lean mass was inversely correlated to fat mass ($r = -0.51$; $P < 0.001$), and BMI was not associated with either measure of liver fat adjusting for age and sex (data not shown). LS ratio had a tendency toward an inverse association with weight ($P = 0.06$) and VAT ($P = 0.06$) adjusting for age, sex, and BMI.

B. Biochemical Variables and Liver Fat

Serum TG, cholesterol, and ALT levels were not associated with liver fat after adjustments for age, sex, and BMI. Fasting glucose level, fasting insulin level, and HOMA-IR were associated with MLA (Fig. 1); however, other measures of glucose metabolism (WBISI, IGI, and oDI) were not related to either measure of liver fat (Table 2). Adiponectin was not associated with liver fat ($P > 0.6$) but was associated with HDL-C (adjusting for age, sex, and BMI: $r = 0.36$; $P = 0.002$). Adiponectin was associated with WBISI ($r = 0.30$; $P = 0.05$) but had no association with HOMA-IR ($P = 0.5$). However, the association between adiponectin and

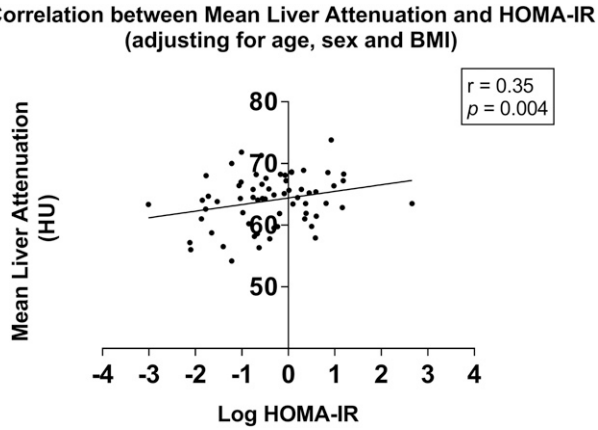

Figure 1. Correlation between mean liver attenuation and HOMA-IR (with adjustments for age, sex, and BMI).

WBISI was nullified by adjustment for BMI ($P = 0.08$) (data not shown). Fetuin-A was not associated with either outcome measure of liver fat ($P = 0.6$), HOMA-IR, WBISI, oDI, or adiponectin (P values > 0.27) (data not shown).

C. Predictors of Liver Fat

In the informal forward variable selection analysis, MLA was associated with fasting glucose ($\beta = 0.28$; $P = 0.05$) and fasting insulin ($\beta = 0.5$; $P = 0.03$) and negatively associated with

Table 2. Correlation of Liver Fat Measures With Body Composition and Biochemical Variables

Body Composition or Biochemical Variable	LS Ratio Adjusted for				Mean Liver Attenuation Adjusted for			
	Age and Sex		Age, Sex, and BMI		Age and Sex		Age, Sex, and BMI	
	r	*P*	*r*	*P*	*r*	*P*	*r*	*P*
Weight	−0.08	0.55	−0.25	0.06	−0.16	0.16	−0.30	0.009
Height	−0.21	0.10	−0.21	0.11	−0.28	0.016	−0.28	0.017
Waist circumference	0.10	0.4	0.07	0.6	−0.01	1.0	−0.05	0.7
Fat mass[a]	0.04	0.8	−0.04	0.8	−0.01	0.9	−0.04	0.7
Lean mass[a]	−0.16	0.2	−0.20	0.1	−0.32	0.005	−0.35	0.003
VAT area[a]	−0.18	0.2	−0.24	0.06	−0.01	1.0	−0.02	0.9
SAT area[a]	−0.10	0.4	−0.18	0.2	0.11	0.3	0.12	0.3
VAT/SAT[a]	−0.01	1.0	0.02	0.9	−0.15	0.2	−0.15	0.2
HDL-C	0.13	0.3	0.15	0.3	0.03	0.8	0.03	0.8
LDL-C	−0.03	0.8	−0.03	0.8	−0.02	0.9	−0.02	0.9
Triglycerides[a]	−0.10	0.4	−0.11	0.4	0.06	0.6	0.06	0.6
ALT[a]	−0.02	0.9	−0.02	0.9	0.10	0.4	0.10	0.4
Adiponectin[a]	0.02	0.9	0.04	0.8	−0.02	0.9	−0.01	0.9
Fetuin-A	−0.07	0.6	−0.06	0.6	−0.06	0.6	−0.06	0.6
Fasting glucose	0.14	0.3	0.14	0.3	0.23	0.04	0.23	0.05
2-h glucose[a]	0.11	0.4	0.11	0.4	0.09	0.5	0.08	0.5
Fasting insulin[a]	0.18	0.2	0.16	0.2	0.38	0.001	0.42	<0.001
HOMA-IR[a]	0.17	0.2	0.15	0.3	0.33	0.007	0.35	0.004
WBISI[a]	−0.12	0.4	−0.10	0.5	−0.04	0.7	−0.04	0.8
Insulinogenic index	0.05	0.7	0.06	0.7	0.19	0.1	0.20	0.1
Oral disposition index[a]	−0.08	0.6	−0.06	0.7	0.02	0.9	0.03	0.8

Abbreviations: *r*, correlation coefficient; *P*, *P* value.
[a]Log-transformed to a normal distribution.

Table 3. Predictors of MLA and LS Ratio in Men and Women

	Unstandardized Coefficient		Standardized Coefficient	
	B[a]	Standard Error	β[b]	*P* Value
MLA, HU				
Constant	69.92	3.83		0.000
Age, y	0.042	0.069	0.07	0.544
Sex	−5.09	1.27	−0.58	0.000
Fasting insulin, μIU/mL	3.12	0.72	0.59	0.000
Adult weight, kg	−0.16	0.06	−0.35	0.008
LS ratio				
Constant	1.218	0.109		0.000
Age, y	−0.001	0.002	−0.048	0.717
Sex	0.023	0.036	0.087	0.537
ALT, IU/L	−0.010	0.037	−0.038	0.785

Nonnormally distributed variables were log-transformed before inclusion in the regression.
[a]The unstandardized coefficient (B) describes the number of units of the outcome associated with a 1-unit change in the predictor.
[b]The standardized coefficient (β) describes the correlation when both the predictor and outcome are expressed in standardized units (*i.e.,* mean = 0, SD = 1).

weight in men ($\beta = -0.5$; $P < 0.001$). In women, MLA was associated with fasting insulin ($\beta = 0.42$; $P = 0.01$) (data not shown). When both sexes were included, MLA had a negative association with weight and a positive association with fasting insulin (Table 3).

In men, LS ratio was associated with fasting glucose ($\beta = 0.39$; $P = 0.03$) and negatively associated with BMI ($\beta = -0.71$; $P < 0.001$), whereas in women, LS ratio was associated with mean waist circumference ($\beta = 0.5$; $P = 0.04$) (data not shown). However, none of the variables was associated with LS ratio after adjustments for sex (Table 3).

3. Discussion

This report describes NAFLD and its metabolic features in a nonobese population of exclusively African origin. As we hypothesized, some of our findings were distinct from those reported in other populations. These include associations between liver fat and reduced HOMA-IR and reduced fasting insulin concentration. In addition, serum TG and LDL-C levels did not show the characteristic associations with liver fat, nor was HDL-C related to liver fat.

Liver fat >30% was found in <4% of participants on the basis of LS ratio ≤1, and we posit several explanations for this low occurrence. Persons of African origin have the lowest burden of NAFLD compared with Hispanics and whites; in a nationally representative sample of the US population, the age-adjusted prevalence of NAFLD was highest in Mexican Americans (21.2%) followed by non-Hispanic whites (12.5%) and was lowest in non-Hispanic blacks (11.6%) [27]. Second, CT is less sensitive at detecting liver fat values <30%. These factors coupled with the young age of our participants likely influenced the low prevalence of fatty liver in our study.

Our findings suggest that the LS ratio is more sensitive than MLA in the detection of liver fat. Similarly, Rogier *et al.* [28] reported that the LS ratio was more accurate than mean liver attenuation for detecting macrovesicular steatosis >30% (area under the curve = 0.94 vs 0.89), with the LS ratio having a higher positive predictive value. In addition, the effects of different CT scanners as well as different reconstruction algorithms on the absolute attenuation value of liver parenchyma varies [29], and these potential errors in measurement of attenuation can be avoided by using spleen attenuation as an internal control. Finally, the seemingly higher sensitivity of the LS ratio may also result from the inclusion of milder cases of hepatic steatosis.

Both LS ratio <1 and MLA ≤40 HU are reported to indicate moderate to severe hepatic steatosis [30, 31], although other studies suggest that different thresholds may be more relevant. Zeb *et al.* [17] demonstrated that the prevalence of fatty liver as estimated by LS ratio <1.0 was higher than that provided by liver attenuation <40 HU (17.2% vs 6.3%), and the MLA corresponding to the prevalence provided by LS ratio <1.0 was <51 HU. Although several other authors have suggested using a higher cutoff for MLA (*i.e.,* 48 HU) to indicate moderate to severe liver fat accumulation [32, 33], it is important to note that utilizing these threshold values did not affect our findings.

A. Body Composition and Liver Fat

Liver fat was associated with body weight and height and had a tendency toward a positive association with VAT but not fat mass. We posit that fat mass in this population may be influenced by higher SAT (reported to be the preferred fat storage depot in persons of African origin) [34]. Although women had twice as much SAT as men, they had comparable liver fat, similar to findings reported by Westerbacka *et al.* [35]. It has been theorized that SAT acts as a metabolically neutral fat reservoir that protects against fat spilling over into ectopic depots such as visceral fat and hepatic fat, which are associated with greater metabolic risk [36].

We demonstrated an association between liver fat (MLA) and height and weight. The unexpected association with lean mass was influenced by the height of the participants; this finding suggests that despite being highly colinear, height (not lean mass) influenced liver fat accumulation in this group. It appears that lean mass acts as a proxy for fat mass in healthy subjects with obesity (who tend to have greater lean mass). As evidence, lean body mass index was associated with liver fat measured by magnetic resonance spectroscopy ($r = 0.28$; $P = 0.002$) among 113 Canadian youth with overweight and obesity [37]. However, the same may not be true among our lean subjects, for whom there was a negative association between lean and fat mass. In contrast, among 11,116 South Korean adults, participants with the least liver fat (as estimated by fatty liver index) showed the highest skeletal muscle mass [38].

B. Biochemical Variables and Liver Fat

As we hypothesized, serum TG and LDL-C levels did not show characteristic associations with liver fat, nor was HDL-C related to liver fat. Persons of African origin are known to have lower mean TG and LDL-C concentrations than whites [39], and the associations between TG concentration and insulin resistance, cardiovascular disease, and type 2 diabetes mellitus are lower in blacks than in other ethnic groups (the TG paradox) [12]. Conversely, among nonobese Koreans, TG levels were significantly associated with both the development and regression of NAFLD [40]. For this reason, our findings may reflect ethnic differences in lipid profiles; thus, indices such as fatty liver index, which use TG concentrations, may not be suitable for estimating liver fat in persons of African origin.

ALT level was similarly unrelated to either outcome measure of liver fat; however, normal ALT values were previously reported in patients across the entire histological spectrum of NAFLD [41, 42], similar to most of our participants. This suggests that benign fat accumulation is occurring in the absence of liver injury (inflammation) with no attendant increase in ALT levels, as most of our participants had ALT concentrations well below the upper limit of normal.

Despite a documented inverse association with liver fat accumulation [43], adiponectin was not associated with liver fat in our participants. Because adiponectin is secreted by adipose tissue, our findings may reflect the lack of an association between fat mass and liver fat in our study population. The study may also have been underpowered to detect an association between adiponectin and liver fat, although the expected associations between adiponectin and HDL-C and insulin sensitivity (WBISI) were demonstrated. Fetuin-A, a hepatokine that suppresses adiponectin production and is increased in persons

with biopsy-proven NAFLD [44], showed no correlation with adiponectin or liver fat in our group. In addition, although fetuin-A is also associated with impaired insulin sensitivity [45] and impaired glucose tolerance [46], we demonstrated no association with HOMA-IR or WBISI. However, it is notable that rs738409, the PNPLA3 variant associated with both fetuin-A concentration and NAFLD [47, 48], is less common in African Americans than in Hispanic Americans (19% vs 40%) [49]. We are not aware of any prior study reporting fetuin-A levels in nonobese individuals with NAFLD, so it is unclear whether our findings are specific to persons of African origin. Nevertheless, the study provided reference data for fetuin-A in our population, with the mean concentration of fetuin-A (0.5 ± 0.1 g/L) being comparable to that reported by Jensen *et al.* [50] (0.43 ± 0.09 g/L) in 542 African Americans aged >65 years.

Of note, in our study population, lower concentrations of fasting glucose and insulin were associated with more liver fat, as was decreased HOMA-IR. These findings are atypical, as associations between nonobese NAFLD and insulin resistance are well documented [51, 52], albeit among middle-aged Asians. Our findings are not without precedence, however, as Hakim *et al.* [53] reported a lack of association between liver fat and hepatic insulin sensitivity in British men of African origin. Lipid intermediates, which accumulate from excessive liver fat, can cause dysfunction of hepatic mitochondria, inflammation, and increased very-low-density lipoprotein–TG production with subsequent hepatic and systemic insulin resistance. However, the unique mechanisms of fat distribution and metabolism that occur in persons of African origin may render these lipid intermediaries less damaging [53]. It is also important to note that our research group previously reported that HOMA-IR has limitations in our population [54] and may be imprecise in lean individuals, and this is supported by the lack of association between WBISI and liver fat.

The inverse relationship between liver fat and insulin concentration may be a consequence of insulin's inhibition of hormone-sensitive lipase, which hydrolyzes fatty acids from triacylglycerols or diacylglycerols. Insulin-resistant African American women have a greater acute insulin response to glucose than insulin-resistant white women after a frequently sampled IV glucose tolerance test [55]. Furthermore, this insulin response was out of proportion to their degree of insulin resistance [55]. It was concluded that this hyperinsulinemia in African American women accounted for the greater FFA clearance observed in African American women [55]. The clear implication is that basal hyperinsulinemia may be an important variable in our population and that relative hyperinsulinemia could thus reduce liver fat accumulation in persons of African origin. In addition, African Americans appear to be more resistant to the accretion of fat in the liver associated with insulin resistance [13], the so-called insulin resistance paradox.

Using forward variable selection, we again identified body weight and reduced fasting insulin as predictors of liver fat (as estimated by MLA). As discussed previously, our findings related to fasting insulin concentrations may be due to ethnic differences in the relative effects of insulin action and insulin sensitivity. Consequently, we cannot rule out our hypothesis that there may be a unique pathogenesis of liver fat accumulation, independent of insulin resistance, in our population.

In the final analysis, it is likely that some of the observed differences in the prevalence and pathogenesis of NAFLD across ethnicities have genetic origins. Although it occurs less frequently in persons of African origin, the *PNPLA3* gene variant (rs738409) is associated with neither HOMA-IR nor concentrations of TG, total cholesterol, HDL-C, or LDL-C [56], and it has a reported significant association with ALT and aspartate aminotransferase only in Hispanics [47]. Lean subjects with NAFLD were shown to have an increased rate of rs738409 carriage compared with their counterparts with obesity (78.4% vs 59.8%; P = 0.001) [57].

Our study has some limitations. The low sensitivity of CT in detecting milder degrees of liver fat may have led to underestimation of the true prevalence of fatty liver disease. However, we believe the cutoff values used in this study are justified, as liver fat accumulation of ~30% is reported to correspond to a liver attenuation of 40 HU [30, 31]. Unenhanced CT is less sensitive than magnetic resonance spectroscopy and MRI, both of which were

unavailable in our center at the time of the study. The potential risk of radiation exposure with CT was minimized by taking two single slices, using a reduced radiation dose, and operating the machine in tissue optimization mode. In addition, the aerobic fitness of our subjects, which could have reduced liver fat, was not accounted for in the study. A final limitation of this study was the modest sample size, which may have resulted in the study being underpowered to detect some associations.

Despite the previous limitations, our study had several strengths. The participants were well characterized using a range of clinical and biochemical variables, and more than one outcome measure of insulin resistance was used. CT scans provided data that were objective, quantitative, and standardized by a phantom and provided the added benefit of objectively measuring visceral fat. In addition, unenhanced CT was conducted to avoid the potential errors of contrast-enhanced CT and the potential toxicity of iodinated contrast material.

4. Conclusion

In summary, we report the characteristics of fatty liver in a nonobese population of African origin. The prevalence of NAFLD and features of metabolic syndrome were low in Afro-Caribbean subjects of normal weight. Liver fat had unexpected associations with lower fasting insulin concentration, suggesting that hyperinsulinemia was influential in reducing liver fat in this population. The extent to which these findings are related to ethnicity, participant age, body size, or the method of estimating liver fat is unknown and warrants clarification. It would therefore be instructive to investigate these variables in a larger group of individuals, using a more sensitive measure of liver fat.

Acknowledgments

We gratefully acknowledge the men and women who participated in this study. In addition, we recognize Joan Patterson-McNamee, Kenesha Pencott-Brown, Hemoy Drummond, Lorraine Wilson, Diahann Knight, and Stacey Chin for their work at the Tropical Metabolism Research Unit, The University of the West Indies, Kingston, Jamaica.

Financial Support: This work was supported by New Zealand Health Research Council grant no. 09/052 (to T.E.F.), Developmental Adaptation to an Obesogenic Environment Program; the Caribbean Public Health Agency (to D.S.T.); and the University of the West Indies Graduate Studies Research and Publications Grant (to D.S.T.). C.D.B. is supported in part by the Southampton NIHR Biomedical Research Centre.

Author Contributions: D.S.T., M.S.B., T.E.F., and C.D.B. designed the research. I.A.T., D.P.S., and D.S.T. participated in data collection and coordinating the clinical samples. C.O. and D.S.T. analyzed the data. D.S.T. conducted the literature review and wrote the first draft of the manuscript, and M.S.B. had responsibility for final content. All authors read, contributed to, and approved the final manuscript.

Additional Information

Correspondence: Debbie S. Thompson, PhD, Caribbean Institute for Health Research, The University of the West Indies, Mona Campus, Kingston 7, Jamaica, West Indies. E-mail: debbie.thompson@uwimona.edu.jm.

Disclosure Summary: The authors have nothing to disclose.

Data Availability: The datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

References and Notes

1. Bedogni G, Miglioli L, Masutti F, Tiribelli C, Marchesini G, Bellentani S. Prevalence of and risk factors for nonalcoholic fatty liver disease: the Dionysos nutrition and liver study. *Hepatology*. 2005;**42**(1): 44–52.

2. Bellentani S, Scaglioni F, Marino M, Bedogni G. Epidemiology of non-alcoholic fatty liver disease. *Dig Dis*. 2010;**28**(1):155–161.
3. Marchesini G, Bugianesi E, Forlani G, Cerrelli F, Lenzi M, Manini R, Natale S, Vanni E, Villanova N, Melchionda N, Rizzetto M. Nonalcoholic fatty liver, steatohepatitis, and the metabolic syndrome. *Hepatology*. 2003;**37**(4):917–923.
4. Aby E, Saab S. Nonobese nonalcoholic fatty liver disease. *Clin Liver Dis (Hoboken)*. 2017;**10**(5):130–133.
5. Kim D, Kim WR. Nonobese fatty liver disease. *Clin Gastroenterol Hepatol*. 2017;**15**(4):474–485.
6. Browning JD, Szczepaniak LS, Dobbins R, Nuremberg P, Horton JD, Cohen JC, Grundy SM, Hobbs HH. Prevalence of hepatic steatosis in an urban population in the United States: impact of ethnicity. *Hepatology*. 2004;**40**(6):1387–1395.
7. Foster T, Anania FA, Li D, Katz R, Budoff M. The prevalence and clinical correlates of nonalcoholic fatty liver disease (NAFLD) in African Americans: the multiethnic study of atherosclerosis (MESA). *Dig Dis Sci*. 2013;**58**(8):2392–2398.
8. Younossi ZM, Stepanova M, Negro F, Hallaji S, Younossi Y, Lam B, Srishord M. Nonalcoholic fatty liver disease in lean individuals in the United States. *Medicine (Baltimore)*. 2012;**91**(6):319–327.
9. Sookoian S, Pirola CJ. Systematic review with meta-analysis: risk factors for non-alcoholic fatty liver disease suggest a shared altered metabolic and cardiovascular profile between lean and obese patients. *Aliment Pharmacol Ther*. 2017;**46**(2):85–95.
10. Kwon YM, Oh SW, Hwang SS, Lee C, Kwon H, Chung GE. Association of nonalcoholic fatty liver disease with components of metabolic syndrome according to body mass index in Korean adults. *Am J Gastroenterol*. 2012;**107**(12):1852–1858.
11. Marchesini G, Brizi M, Bianchi G, Tomassetti S, Bugianesi E, Lenzi M, McCullough AJ, Natale S, Forlani G, Melchionda N. Nonalcoholic fatty liver disease: a feature of the metabolic syndrome. *Diabetes*. 2001;**50**(8):1844–1850.
12. Yu SS, Castillo DC, Courville AB, Sumner AE. The triglyceride paradox in people of African descent. *Metab Syndr Relat Disord*. 2012;**10**(2):77–82.
13. Guerrero R, Vega GL, Grundy SM, Browning JD. Ethnic differences in hepatic steatosis: an insulin resistance paradox? *Hepatology*. 2009;**49**(3):791–801.
14. Kumar R, Mohan S. Non-alcoholic fatty liver disease in lean subjects: characteristics and implications. *J Clin Transl Hepatol*. 2017;**5**(3):216–223.
15. Tanaka S, Horimai C, Katsukawa F. Ethnic differences in abdominal visceral fat accumulation between Japanese, African-Americans, and Caucasians: a meta-analysis. *Acta Diabetol*. 2003;**40**(Suppl 1):s302–s304.
16. Francis-Emmanuel PM, Thompson DS, Barnett AT, Osmond C, Byrne CD, Hanson MA, Gluckman PD, Forrester TE, Boyne MS. Glucose metabolism in adult survivors of severe acute malnutrition. *J Clin Endocrinol Metab*. 2014;**99**(6):2233–2240.
17. Zeb I, Li D, Nasir K, Katz R, Larijani VN, Budoff MJ. Computed tomography scans in the evaluation of fatty liver disease in a population based study: the multi-ethnic study of atherosclerosis. *Acad Radiol*. 2012;**19**(7):811–818.
18. Boyne MS, Thame M, Osmond C, Fraser RA, Gabay L, Reid M, Forrester TE. Growth, body composition, and the onset of puberty: longitudinal observations in Afro-Caribbean children. *J Clin Endocrinol Metab*. 2010;**95**(7):3194–3200.
19. RRID:AB_2801438, https://scicrunch.org/resolver/AB_2801438.
20. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem*. 1972;**18**(6):499–502.
21. RRID:AB_2801457, https://scicrunch.org/resolver/AB_2801457.
22. RRID:AB_2801458, https://scicrunch.org/resolver/AB_2801458.
23. Paschos P, Paletas K. Non alcoholic fatty liver disease and metabolic syndrome. *Hippokratia*. 2009; **13**(1):9–19.
24. Wang L, Wang W, Xu L, Cheng X, Ma Y, Liu D, Guo Z, Su Y, Wang Q. Relation of visceral and subcutaneous adipose tissue to bone mineral density in Chinese women. *Int J Endocrinol*. 2013;**2013**: 378632.
25. Wallace TM, Levy JC, Matthews DR. Use and abuse of HOMA modeling. *Diabetes Care*. 2004;**27**(6): 1487–1495.
26. WHO. Diabetes Mellitus: Report of a WHO Study Group. Geneva, Switzerland: World Health Organization; 1985.
27. Schneider ALC, Lazo M, Selvin E, Clark JM. Racial differences in nonalcoholic fatty liver disease in the U.S. population. *Obesity (Silver Spring)*. 2014;**22**(1):292–299.

28. Rogier J, Roullet S, Cornélis F, Biais M, Quinart A, Revel P, Bioulac-Sage P, Le Bail B. Noninvasive assessment of macrovesicular liver steatosis in cadaveric donors based on computed tomography liver-to-spleen attenuation ratio. *Liver Transpl*. 2015;**21**(5):690–695.
29. Birnbaum BA, Hindman N, Lee J, Babb JS. Multi-detector row CT attenuation measurements: assessment of intra- and interscanner variability with an anthropomorphic body CT phantom. *Radiology*. 2007;**242**(1):109–119.
30. Park SH, Kim PN, Kim KW, Lee SW, Yoon SE, Park SW, Ha HK, Lee MG, Hwang S, Lee SG, Yu ES, Cho EY. Macrovesicular hepatic steatosis in living liver donors: use of CT for quantitative and qualitative assessment. *Radiology*. 2006;**239**(1):105–112.
31. Kodama Y, Ng CS, Wu TT, Ayers GD, Curley SA, Abdalla EK, Vauthey JN, Charnsangavej C. Comparison of CT methods for determining the fat content of the liver. *AJR Am J Roentgenol*. 2007; **188**(5):1307–1312.
32. Bydder GM, Chapman RW, Harry D, Bassan L, Sherlock S, Kreel L. Computed tomography attenuation values in fatty liver. *J Comput Tomogr*. 1981;**5**(1):33–35.
33. Yajima Y, Narui T, Ishii M, Abe R, Ohtsuki M, Goto Y, Endo S, Yamada K, Ito M. Computed tomography in the diagnosis of fatty liver: total lipid content and computed tomography number. *Tohoku J Exp Med*. 1982;**136**(3):337–342.
34. Katzmarzyk PT, Bray GA, Greenway FL, Johnson WD, Newton RL Jr, Ravussin E, Ryan DH, Smith SR, Bouchard C. Racial differences in abdominal depot-specific adiposity in white and African American adults. *Am J Clin Nutr*. 2010;**91**(1):7–15.
35. Westerbacka J, Cornér A, Tiikkainen M, Tamminen M, Vehkavaara S, Häkkinen AM, Fredriksson J, Yki-Järvinen H. Women and men have similar amounts of liver and intra-abdominal fat, despite more subcutaneous fat in women: implications for sex differences in markers of cardiovascular risk. *Diabetologia*. 2004;**47**(8):1360–1369.
36. Boyne MS, Bennett NR, Cooper RS, Royal-Thomas TY, Bennett FI, Luke A, Wilks RJ, Forrester TE. Sex-differences in adiponectin levels and body fat distribution: longitudinal observations in Afro-Jamaicans. *Diabetes Res Clin Pract*. 2010;**90**(2):e33–e36.
37. Sénéchal M, Wicklow B, Wittmeier K, Hay J, MacIntosh AC, McGavock JM. Is lean body mass index associated with liver fat in youth at risk of type 2 diabetes? *Can J Diabetes*. 2013;**37**(6):434.
38. Moon JS, Yoon JS, Won KC, Lee HW. The role of skeletal muscle in development of nonalcoholic fatty liver disease. *Diabetes Metab J*. 2013;**37**(4):278–285.
39. Mcintosh MS, Kumar V, Kalynych C, Lott M, Hsi A, Chang JL, Lerman RH. Racial differences in blood lipids lead to underestimation of cardiovascular risk in black women in a nested observational study. *Glob Adv Health Med*. 2013;**2**(2):76–79.
40. Kim NH, Kim JH, Kim YJ, Yoo HJ, Kim HY, Seo JA, Kim NH, Choi KM, Baik SH, Choi DS, Kim SG. Clinical and metabolic factors associated with development and regression of nonalcoholic fatty liver disease in nonobese subjects. *Liver Int*. 2014;**34**(4):604–611.
41. Mofrad P, Contos MJ, Haque M, Sargeant C, Fisher RA, Luketic VA, Sterling RK, Shiffman ML, Stravitz RT, Sanyal AJ. Clinical and histologic spectrum of nonalcoholic fatty liver disease associated with normal ALT values. *Hepatology*. 2003;**37**(6):1286–1292.
42. Fracanzani AL, Valenti L, Bugianesi E, Andreoletti M, Colli A, Vanni E, Bertelli C, Fatta E, Bignamini D, Marchesini G, Fargion S. Risk of severe liver disease in nonalcoholic fatty liver disease with normal aminotransferase levels: a role for insulin resistance and diabetes. *Hepatology*. 2008;**48**(3):792–798.
43. Pagano C, Soardo G, Esposito W, Fallo F, Basan L, Donnini D, Federspil G, Sechi LA, Vettor R. Plasma adiponectin is decreased in nonalcoholic fatty liver disease. *Eur J Endocrinol*. 2005;**152**(1):113–118.
44. Haukeland JW, Dahl TB, Yndestad A, Gladhaug IP, Løberg EM, Haaland T, Konopski Z, Wium C, Aasheim ET, Johansen OE, Aukrust P, Halvorsen B, Birkeland KI. Fetuin A in nonalcoholic fatty liver disease: *in vivo* and *in vitro* studies. *Eur J Endocrinol*. 2012;**166**(3):503–510.
45. Mori K, Emoto M, Yokoyama H, Araki T, Teramura M, Koyama H, Shoji T, Inaba M, Nishizawa Y. Association of serum fetuin-A with insulin resistance in type 2 diabetic and nondiabetic subjects. *Diabetes Care*. 2006;**29**(2):468.
46. Ou H-Y, Yang Y-C, Wu H-T, Wu J-S, Lu F-H, Chang C-J. Increased fetuin-A concentrations in impaired glucose tolerance with or without nonalcoholic fatty liver disease, but not impaired fasting glucose. *J Clin Endocrinol Metab*. 2012;**97**(12):4717–4723.
47. Romeo S, Kozlitina J, Xing C, Pertsemlidis A, Cox D, Pennacchio LA, Boerwinkle E, Cohen JC, Hobbs HH. Genetic variation in PNPLA3 confers susceptibility to nonalcoholic fatty liver disease. *Nat Genet*. 2008;**40**(12):1461–1465.

48. Rametta R, Ruscica M, Dongiovanni P, Macchi C, Fracanzani AL, Steffani L, Fargion S, Magni P, Valenti L. Hepatic steatosis and PNPLA3 I148M variant are associated with serum fetuin-A independently of insulin resistance. *Eur J Clin Invest*. 2014;**44**(7):627–633.
49. Wagenknecht LE, Palmer ND, Bowden DW, Rotter JI, Norris JM, Ziegler J, Chen YD, Haffner S, Scherzinger A, Langefeld CD. Association of *PNPLA3* with non-alcoholic fatty liver disease in a minority cohort: the Insulin Resistance Atherosclerosis Family Study. *Liver Int*. 2011;**31**(3):412–416.
50. Jensen MK, Bartz TM, Djoussé L, Kizer JR, Zieman SJ, Rimm EB, Siscovick DS, Psaty BM, Ix JH, Mukamal KJ. Genetically elevated fetuin-A levels, fasting glucose levels, and risk of type 2 diabetes: the cardiovascular health study. *Diabetes Care*. 2013;**36**(10):3121–3127.
51. Sinn DH, Gwak GY, Park HN, Kim JE, Min YW, Kim KM, Kim YJ, Choi MS, Lee JH, Koh KC, Paik SW, Yoo BC. Ultrasonographically detected non-alcoholic fatty liver disease is an independent predictor for identifying patients with insulin resistance in non-obese, non-diabetic middle-aged Asian adults. *Am J Gastroenterol*. 2012;**107**(4):561–567.
52. Omagari K, Kadokawa Y, Masuda J, Egawa I, Sawa T, Hazama H, Ohba K, Isomoto H, Mizuta Y, Hayashida K, Murase K, Kadota T, Murata I, Kohno S. Fatty liver in non-alcoholic non-overweight Japanese adults: incidence and clinical characteristics. *J Gastroenterol Hepatol*. 2002;**17**(10): 1098–1105.
53. Hakim O, Bello O, Bonadonna RC, Mohandas C, Shojaee-Moradie F, Jackson N, Boselli L, Whitcher B, Shuaib H, Alberti KGMM, Peacock JL, Umpleby AM, Charles-Edwards G, Amiel SA, Goff LM. Ethnic differences in intrahepatic lipid and its association with hepatic insulin sensitivity and insulin clearance between men of black and white ethnicity with early type 2 diabetes. *Diabetes Obes Metab*. 2019;**21**(9):2163–2168.
54. Thompson DS, Boyne MS, Osmond C, Ferguson TS, Tulloch-Reid MK, Wilks RJ, Barnett AT, Forrester TE. Limitations of fasting indices in the measurement of insulin sensitivity in Afro-Caribbean adults. *BMC Res Notes*. 2014;**7**(1):98.
55. Chow CC, Periwal V, Csako G, Ricks M, Courville AB, Miller BV III, Vega GL, Sumner AE. Higher acute insulin response to glucose may determine greater free fatty acid clearance in African-American women. *J Clin Endocrinol Metab*. 2011;**96**(8):2456–2463.
56. Pan JJ, Fallon MB. Gender and racial differences in nonalcoholic fatty liver disease. *World J Hepatol*. 2014;**6**(5):274–283.
57. Wei JL, Leung JC, Loong TC, Wong GL, Yeung DK, Chan RS, Chan HL, Chim AM, Woo J, Chu WC, Wong VW. Prevalence and severity of nnalcoholic fatty liver disease in non-obese patients: a population study using proton-magnetic resonance spectroscopy. *Am J Gastroenterol*. 2015;**110**(9):1306–1314, quiz 1315.