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Skeletal Muscle Adiposity is associated with Serum Lipid and Lipoprotein Levels in Afro-Caribbean Men

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Abstract

Objective—Compared to other ethnic groups, African ancestry individuals have lower triglycerides and higher HDL-C levels, although the mechanisms for these differences remain unclear. Our objective was to evaluate a comprehensive array of factors potentially related to fasting serum lipid and lipoprotein levels in African ancestry men.

Design and Methods—1821 men underwent DXA measures of total body fat and quantitative computed tomography assessments of calf skeletal muscle adiposity (subcutaneous and intermuscular adipose tissue (AT), and muscle density as a measure of intra-muscular AT).

Results—Multivariable linear regression analysis identified age (–), total body fat (+), subcutaneous AT (–), fasting glucose (+), fasting insulin (+), diastolic blood pressure (+) and non-African ancestry (+) as independent correlates of triglycerides (all $P < 0.05$). Total body fat (+), intra-muscular AT (–) and diastolic blood pressure (+) were independent correlates of LDL-C (all $P < 0.001$). Age (+), waist circumference (–), fasting insulin (–), physical activity (+) and alcohol intake (+) were independent correlates of HDL-C (all $P < 0.05$).

Conclusions—Our study illuminates a novel relationship between skeletal muscle adiposity and serum lipid and lipoprotein levels in African ancestry men, independent of total and central adiposity. Our finding also suggests that in African ancestry populations, genetic factors are likely a significant determinant of triglycerides levels.

Keywords

Skeletal Muscle; Adiposity; Lipids; Lipoprotein; African

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Introduction

Elevated serum triglyceride concentrations (TG) and low HDL-C are strongly associated with obesity, hypertension, and type 2 diabetes mellitus (T2DM)[1], metabolic disorders that are highly prevalent in populations of African ancestry [2]. Paradoxically, African ancestry individuals are less likely to have elevated TG and low HDL-C levels compared to other ethnic groups [3]. Although there have been some hypotheses proposed to explain this paradox [4], the physiological mechanisms and factors responsible for the favorable lipoprotein profile in African ancestry individuals remain poorly documented. Large studies across populations of African ancestry living outside of the U.S. are needed, as the data derived from studies in African-Americans may be confounded by their high degrees of westernization and non-African admixture.

The strong impact of obesity and adiposity on serum lipids and lipoproteins is well established [5]. An increased accumulation of visceral and ectopic adipose tissue (AT) in skeletal muscle, liver and heart may be a more important determinant of the serum lipoprotein profile than excess adiposity per se [6]. In particular, emerging evidence indicates that accumulation of AT in skeletal muscle increases with aging, is greater in African ancestry than in white men, and significantly contributes to the development of metabolic syndrome and T2DM, independent of general obesity [7]. While the association between visceral AT and the serum lipoprotein profile is well established [8], very little is known about the association between skeletal muscle adiposity and serum lipid and lipoproteins. Therefore, in the current study we examined the relationship between skeletal muscle adiposity and fasting serum lipid and lipoprotein levels, and tested if these relationships were independent of obesity, T2DM and other medical and lifestyle factors in a large cohort of middle-aged and elderly Afro-Caribbean men.

Materials and Methods

Study Population

Between 1998 and 2003, 3170 men aged 40 and older on the Caribbean island of Tobago were recruited for a population-based prostate specific antigen screening study. To be eligible, men had to be ambulatory, non-institutionalized and not terminally ill. Recruitment for the survey was accomplished by flyers, public service announcements, posters, informing health care workers at local hospital and health centers, and word of mouth. Approximately 60% of all age-eligible men on the island participated and participation was representative of the island Parishes. The recruited cohort was 97% African, 2% East Indian, <1% white, and <1% "other" as defined by participant-report of paternal and maternal grandparents' ethnicity. Ancestry informative genetic markers have confirmed a low admixture (6% non-African ancestry) in this population [9] compared to the African-American population which has a higher degree of admixture (~18.5%) [10]. Written informed consent was obtained from all study participants using forms approved by the Institutional Review Boards of the University of Pittsburgh and the Tobago Division of Health and Social Services.

Analytic Sample

In 2004, body composition was assessed at a follow-up examination by peripheral quantitative computed tomography (pQCT) and dual-energy X-ray absorptiometry (DXA) in 2,031 men in the cohort (70% of survivors) and 451 new participants who were recruited using similar methods. From the 2,482 men with complete DXA and pQCT adiposity and anthropometric measures, demographic and lifestyle information, and medical history, we excluded men who were missing serum metabolic assay data (n=661), leaving an analytic cohort of 1821 men. All of these men reported 4 grandparents of African ancestry. There were no differences in age, DXA and pQCT adiposity and anthropometric measures, and obesity, type 2 diabetes mellitus, and hypertension status between men with available serum lipid and lipoprotein levels (random sample of 1821) and those without these measures.

Biochemical Measurements

All biochemical assays were performed in the Heinz Nutrition Laboratory at the University of Pittsburgh's Graduate School of Public Health which has met the accuracy and precision standards of the Centers for Disease Control and Prevention and is Clinical Laboratory Improvement Amendment (CLIA) accredited. Serum was prepared after morning, fasting phlebotomy and stored at -70°C until assay. HDL-C was determined using the selective heparin/manganese chloride precipitation method, interassay CV 2.1%. LDL-C was calculated by means of the Friedewald equation. Triglycerides were determined enzymatically using the procedure of Bucolo and David, interassay CV 1.7%. Fasting serum glucose was measured using an enzymatic procedure, interassay CV 1.8%. Insulin was measured using an RIA procedure developed by Linco Research, Inc. interassay CV 2.1%. The degree of insulin resistance was estimated by HOMA-IR which was calculated as: $\text{fasting serum glucose (mmol/L)} * \text{fasting serum insulin } (\mu\text{U/mL}) / 22.5$.

Anthropometric, Total Body Fat and Skeletal Muscle Composition Measures

Height was measured to the nearest 0.1 cm using a wall-mounted stadiometer. Body weight was recorded to the nearest 0.1 kg without shoes on a balance beam scale. Body mass index was calculated from height and weight (kg/m^2). Waist circumference was measured at the narrowest point of the waist using an inelastic fiberglass tape. If there was no narrowest point, waist circumference was measured at the umbilicus.

Total body fat was measured by dual-energy X-ray absorptiometry using a Hologic QDR 4500W densitometer (Hologic Inc., Bedford MA). Scans were analyzed with QDR software version 8.26a.

A pQCT scan of the calf was performed using the Stratec XCT-2000 scanner (Orthometrix, Inc.; White Plains, NY) in order to evaluate the total, skeletal muscle, and AT cross-sectional areas. Scans were obtained at 66% of the calf length, proximal to the terminal end of the tibia. Images of the cross-sectional area of skeletal muscle and AT were analyzed using the Stratec analysis software version 5.5D (Orthometrix, Inc., White Plains, NY). We obtained measures of the total AT (mm^2), subcutaneous AT (mm^2), intermuscular AT (i.e. AT beneath the fascia lata; mm^2), total muscle area (mm^2), and muscle density (mg/cm^3). Muscle density reflects the AT content of skeletal muscle such that greater AT infiltration is

associated with lower muscle density [11]. The coefficients of variation (CV) for pQCT skeletal muscle composition measures were determined by repeat pQCT scanning in 15 individuals. The CVs for total AT, subcutaneous AT, intermuscular AT, total muscle area, and muscle density were 0.98%, 1.5%, 7.6%, 3.4%, and 1.1%, respectively.

Spearman correlation coefficients among all adiposity measures used in our analyses were calculated and are shown in Supplementary Table 1. All adiposity measures demonstrated moderate to high correlation (all $P < 0.0001$).

Blood Pressure Measurements

Blood pressures were measured from participants' right arm using an automatic sphygmomanometer OMRON HEM705CP (Omron Healthcare, Inc, Vernon Hills, IL) after they were seated at rest for 5 min. After selecting the proper cuff size on the basis of right midarm circumference, blood pressure was measured three times within an examination visit, with 5 minutes rest time in between the measurements. The first reading was discarded and the average of the second and third reading was used in the analysis.

Lifestyle Correlates and Medication Use

Information on lifestyle habits, demographic information, medical conditions, and medication use, were also assessed using interviewer-administered questionnaires. Alcohol drinking frequency (never, less than one drink per week, 1–3, 4–7, 8–14, 15–21, 22–27, 28, drinks per week) and hours of TV watching, as a measure of sedentary lifestyle, (0, 1–6, 7–13, 14–20, 21–27, 28, hours of TV watching per week) were self-reported in predefined categories. We arbitrarily created two categories of alcohol use (≤ 3 and >3 drinks per week) and TV viewing (<14 and ≥ 14 hours/week). Self-reported information was recorded for current smoking. Self-reported information on walking was recorded as walking is the predominant form of physical activity on the island of Tobago. Questions related to walking habits were phrased to mainly assess "leisure-time walking" (walking for exercise or leisure).

Health Status

Obesity was defined as $\text{BMI} \geq 30 \text{ kg/m}^2$. T2DM was defined as fasting serum glucose $\geq 126 \text{ mg/dl}$ or currently taking anti-diabetic medication. Hypertension was defined as a systolic blood pressure of $\geq 140 \text{ mmHg}$ and/or diastolic blood pressure of $\geq 90 \text{ mmHg}$ or currently taking antihypertensive medication. Elevated TG was defined as a TG level $\geq 150 \text{ mg/dl}$, and low HDL-C was defined as $\text{HDL-C} < 40 \text{ mg/dl}$.

Admixture

We assessed potential population substructure (or ancestry) by genotyping a panel of 119 validated single nucleotide polymorphisms (SNPs) that are highly informative for distinguishing European and African ancestry [12]. Genotyping was completed by Sequenom MassARRAY iPLEX Gold technology (Sequenom, Inc; San Diego, CA) with PCR primers purchased from Invitrogen (Carlsbad, CA). These SNPs were used to model population substructure and obtain a multidimensional 'ancestry' score for each individual, which was based on principal component (PC) analyses [13]. Principal components were

derived from these SNPs for all of the participants and then plotted against each other to identify substructure and outliers. Two principal components are sufficient to account for unknown population admixture [13]. We then classified individuals as “admixed” if one or both of their first two PCs were 2 or more standard deviations from the mean PC value of the cohort.

Statistical Analyses

Prior to statistical analysis the distributions of all traits were assessed for non-normality. Triglycerides were transformed using natural logarithms. Using linear regression analysis, we first evaluated the age-adjusted association of each measured factor with serum lipid and lipoprotein levels. The relationships with potential correlates were expressed as one unit for categorical variables or 1 SD for continuous variables, along with 95% confidence intervals (CIs). To identify the independent correlates of lipid and lipoprotein levels, multiple linear regression analysis was performed. Variables with $p < 0.10$ in the age-adjusted univariate linear regression model were entered into the multiple variable model. In order to ensure proper modeling of adiposity, we used four models of total or central adiposity (BMI, waist circumference, DXA total body fat, pQCT total calf adipose tissue area) and tested subcutaneous or intermuscular AT in each model. The model with the best goodness-of-fit statistic, out of the eight models tested, is presented as the final model for each lipid and lipoprotein measure. The Statistical Analysis System (SAS, version 9.2.; SAS Institute, Cary, NC) and the Statistical Package for the Social Sciences (SPSS version 19.0; IBM Corporation, Somers, NY) were used for statistical analysis.

Results

General Characteristics of Participants

Table 1 shows the general characteristics of participants. The mean age of the men was 58 years (range, 40–92 years). The mean values (\pm SD) for TG (geometric mean), LDL-C and HDL-C were: 99.5 ± 1.4 , 132.6 ± 40.0 and 49.8 ± 13.0 mg/dl, respectively (data not shown). Elevated TG, defined as a TG level ≥ 150 mg/dl, was present in 17.5%, whereas low HDL-C, defined as $\text{HDL-C} < 40$ mg/dl, was present in 22.6% of men (data now shown). Although, on average, participants were moderately overweight as measured by BMI (27.5 kg/m^2), their mean body fat percent was low (20.8%). Twenty four percent of the men were obese, 20.5% had type 2 diabetes mellitus and almost 49% had hypertension. Ten percent of participants drank more than 3 alcoholic drinks per week, 10.6% currently smoked, whereas only 4% of participants used lipid-lowering drugs on a regular basis. Despite the high prevalence of hypertension, current use of anti-hypertensive treatment was reported by only 23% of men. The prevalence of non-African ancestry was 3.1%, despite the fact that all of the participants reported all 4 grandparents to be of African ancestry.

Age-adjusted Regression Results

First, we examined the correlates of lipids and lipoproteins in age-adjusted regression models (Table 1). In a non-adjusted model, each 10 years increase in age was associated with 1.4 mg/dl greater HDL-C ($P < 0.001$). The presence of non-African ancestry was associated with 4.1 mg/dl greater TG levels ($P < 0.05$). The majority of obesity-related

variables were positively correlated with TG and LDL-C, and negatively associated with HDL-C after adjusting for age. Among the traditional obesity-related measures (BMI, waist circumference and total body fat %), the strongest association was observed for DXA total body fat. Each SD (5.9%) increase in DXA total body fat was associated with 3.5 mg/dl greater TG, 8.5 mg/dl greater LDL-C and 4 mg/dl lower HDL-C levels (all $P < 0.05$).

Calf subcutaneous AT and skeletal muscle area were positively correlated with TG and LDL-C, and negatively with HDL-C. Each SD (677 mm²) increase in subcutaneous AT was associated with 1.9 mg/dl greater TG, 6.1 mg/dl greater LDL-C and 3.0 mg/dl lower HDL-C levels (all $P < 0.05$), whereas each SD (1331 mm²) increase in skeletal muscle area was associated with 1.1 mg/dl greater TG, 2.1 mg/dl greater LDL-C and 2.2 mg/dl lower HDL-C levels (all $P < 0.05$). In addition, skeletal muscle AT infiltration, as measured by both greater intermuscular AT and lower skeletal muscle density, were associated with lower HDL-C levels. Each SD (369 mm²) increase in intermuscular AT was associated with 1.1 mg/dl lower HDL-C levels, and each SD (369 mm²) increase in skeletal muscle density was associated with 1.4 mg/dl greater HDL-C levels (all $P < 0.05$).

All T2DM-related measures were positively correlated with TG and LDL-C, and negatively with HDL-C. The associations with lipoprotein levels were slightly stronger for insulin and HOMA-IR than for glucose. For example, every 6.8 μ U/ml increase in fasting insulin was associated with 3 mg/dl greater TG, 4.3 mg/dl greater LDL-C and 3.1 mg/dl lower HDL-C levels (all $P < 0.05$). Both systolic (SBP) and diastolic (DBP) blood pressure were positively associated with TG and LDL-C, but not with HDL-C, with the strongest associations observed between blood pressure and LDL-C. Every 23 mmHg increase in SBP was associated with 3.7 mg/dl greater LDL-C, whereas every 13 mmHg increase in DBP was associated with 4.3 mg/dl greater LDL-C (all $P < 0.05$).

Men who walked more than 3 times per week had 1.3 mg/dl lower TG and 2.5 mg/dl greater HDL-C than those who walked more rarely. In contrast, men who watched television for 14 or more hours per week had 1.4 mg/dl greater TG and 4.3 mg/dl greater LDL-C. Men who smoked had 7.6 mg/dl lower LDL-C and 3 mg/dl greater HDL-C levels compared with nonsmokers, whereas men who regularly drank alcohol had 6.5 mg/dl greater HDL-C. With every 77 mg of caffeine intake per day TG increased by 0.75 mg/dl (All $P < 0.05$).

Obesity and hypertension were positively associated with TG and LDL-C and inversely with HDL-C (All $P < 0.001$). T2DM was associated positively with TG and inversely with HDL-C (All $P < 0.05$), but there was no association with LDL-C. Use of hypoglycemic drugs was associated with lower HDL-C levels, use of lipid-lowering drugs with greater levels of TG and LDL-C, and use of antihypertensive drugs with greater levels of TG and LDL-C and lower HDL-C (All $P < 0.05$).

Correlates of Serum Lipid and Lipoprotein Levels by TG, LDL-C, and HDL-C Quartiles

The distribution of serum lipid and lipoprotein levels by quartiles of TG, LDL-C, and HDL-C, adjusted for age, is shown in Supplementary Tables 2–4. With the exception of skeletal muscle density and skeletal muscle area, which were not significantly different across LDL-C quartiles despite their significant positive association with LDL-C observed in age-

adjusted regression analysis, there were no other significant differences in correlates of serum lipid and lipoprotein levels across quartiles that were not observed in age-adjusted regression analyses. However, the multivariable-adjusted means of skeletal muscle density increased by quartiles of LDL-C ($P < 0.05$, Supplementary Figure 1).

Multivariable Regression Results

We further tested the potential independent associations with serum lipid and lipoproteins using multivariable linear regression analysis (Table 2). The model with the best goodness-of-fit statistic is presented as the final model. Age (-), DXA total body fat (+), subcutaneous AT (-), glucose (+), insulin (+), DBP (+) and non-African ancestry (+) were independently associated with TG, and collectively explained 17% of the variation in TG. DXA total body fat (+), skeletal muscle density (+) and DBP (+) were independently associated with LDL-C and collectively explained 6% of the variation in LDL-C. Finally, age (+), waist circumference (-), insulin (-), walking more than 3 times per week (+) and regular alcohol intake of more than 3 drinks per week (+) were independently associated with HDL-C and explained 16% of its variation. To avoid multi-collinearity, we tested fasting glucose and insulin (shown in Table 2) separately from HOMA-IR in multivariable linear regression models. Like glucose and insulin, HOMA-IR was associated positively with TG and inversely with HDL-C and showed similar final multivariable model results (data not shown).

Correlates of TG/HDL ratio and non-HDL-C

Additionally, we examined the age-adjusted correlates of the TG/HDL-C ratio, a marker for insulin resistance [14], and non-HDL-C, a marker of elevated VLDL cholesterol, TG-rich lipoprotein, or remnant lipoprotein [15] (Supplementary Table 5). The mean values (\pm SD) for TG/HDL-C ratio, and non-HDL-C were: 2.5 ± 1.7 and 154.6 ± 43.7 mg/dl, respectively (data not shown). The patterns of age-adjusted associations between TG/HDL-C ratio and studied correlates were similar as those observed with TG, with the exception of a positive association of TG/HDL-C ratio with intermuscular AT, and a negative association with muscle density, current smoking, and current alcohol intake, which were not observed in our age-adjusted analyses of TG. Age (-), DXA total body fat (+), subcutaneous AT (-), glucose (+), insulin (+), and DBP (+) were independently associated with TG/HDL-C ratio (Supplementary Table 6). Like insulin, HOMA-IR was associated positively with TG/HDL-C ratio in a separate multivariable model ($P < 0.001$, data not shown). Although subcutaneous AT was associated with non-HDL-C after adjusting for age (Supplementary Table 5), we found no novel associations between nonHDL-C and any of the skeletal muscle adiposity measures in multivariable model (Supplementary Table 5). Only total body fat percent (+), fasting glucose (+), and DBP (+) appear to be independent correlates of nonHDL-C in this Afro-Caribbean male population.

The Associations of Skeletal Muscle Adiposity with T2DM

Lastly, considering that subcutaneous AT was found to be an independent correlate of TG/HDL-C ratio in our study, and that a number of previous studies suggested that skeletal muscle adiposity may be a risk factor for T2DM and insulin resistance, independent of general obesity [7], we thought it would be of interest to additionally test for an association

between skeletal muscle adiposity and T2DM (Supplementary Table 7). After adjusting for age and height, no difference in calf total AT and calf muscle area between Afro-Caribbean men with and without T2DM was observed. Importantly, in this Afro-Caribbean population calf subcutaneous AT was lower, intermuscular AT was greater, and skeletal muscle was less dense in diabetics than in non-diabetics (all $p < 0.01$), independent of age, height, DXA total body fat, and pQCT muscle area (Supplementary Table 7).

Discussion

The underlying mechanisms for low levels of serum TG and high levels of HDL-C in African ancestry populations across the world, even in the presence of obesity and type 2 diabetes mellitus, remain unclear. Elevated TG was present in only 17.5% whereas low HDL-C was present in 22.6% of the middle-aged and elderly African ancestry men in our cohort. These prevalence estimates are consistent with the results from other studies in African ancestry men of similar age [16]. To better understand the factors associated with the serum lipid and lipoprotein profile in African ancestry individuals, we comprehensively assessed several conventional and novel factors in our cohort. We found a previously unrecognized, inverse relationship between skeletal muscle AT infiltration and serum LDL-C, and an inverse association of subcutaneous AT with serum triglyceride levels and TG/HDL-C ratio. Our findings also suggest that the degree of non-African ancestry is an independent and strong correlate of serum TG levels in this African ancestry population, despite their very low level of admixture. Finally, we found total body fat and waist circumference to be stronger obesity-related correlates of serum lipid and lipoprotein levels than BMI in this African ancestry male population.

Although obesity is a recognized risk factor for dyslipidemia, the strength of the relationship between obesity and serum lipids and lipoproteins is variable and inconsistent in African ancestry individuals [17]. It is possible that other AT depots such as abdominal visceral and subcutaneous AT, or ectopic AT accumulation in non-adipose tissues may be more important obesity-related risk factors for the development of dyslipidemia. Increased ectopic liver AT was an important correlate of lipoprotein levels in some studies [18]. An exercise related loss of leg intermuscular AT was associated with increased HDL-C and LDL particle size in men, but not in women in another study [19]. However, participants in this study were sedentary, obese, predominantly Caucasian, and investigators focused solely on exercise effects, and did not study serum TG levels. Although we found significant associations of intermuscular AT, skeletal muscle density, and skeletal muscle area with serum lipids and lipoproteins in age-adjusted models, these associations were not independent of the effect of other correlates. Several investigators have suggested that subcutaneous AT stored in the legs plays an important role as a reservoir for excess TG in periods of high energy intake, and thus, prevents increased ectopic AT accumulation within skeletal muscle and other organs [20]. Our findings are in agreement with this hypothesis as in our study population subcutaneous AT was inversely associated with TG independent of total body fat and other significant correlates

In addition, we found a strong positive and independent association between skeletal muscle density and LDL-C. This association may be driven by the less dense, more favorable large

LDL particle subfraction. Serum TG levels in this population were relatively low, and previous studies have shown that individuals with low TG levels, and individuals of African ancestry in general, are characterized by a relative absence of dense small LDL particles [21]. Additionally, this finding could be confounded by anti-hypertensive drug use (diuretics and beta-blockers) and its adverse effects on serum LDL-C [22]. However, when we controlled for anti-hypertensive drug use in multivariable analyses (data not shown), the results remained the same. Further studies are needed to better understand the relationship between skeletal muscle AT infiltration (muscle density) and serum lipoprotein concentrations.

In our study total body fat percentage was a stronger obesity-related correlate of TG, LDL-C, TG/HDL-C ratio, and non HDL-C than BMI and waist circumference, although the strength of an association with total body fat was weakest for TG. In contrast, waist circumference was the strongest obesity-related correlate of HDL-C. Previous studies in African-American men have also found that waist circumference is more strongly associated with HDL-C than total body fat percentage, while the association with BMI seems to be the weakest [23]. Others report a lack of association of obesity measures with TG in African-American men, and a stronger association of TG with obesity measures in white men when compared with African-American men [17]. The strength of the relationship between LDL-C and obesity seems to be variable and inconsistent in African ancestry individuals [24]. The majority of previous studies focused on African-American men only, and examined the association between serum lipid and lipoproteins and anthropometric traits, but not with DXA measured total body fat.

Notably, we also found a strong positive association between the degree of non-African ancestry and serum TG levels. However, we did not observe the association between the degree of non-African ancestry and TG/HDL-C ratio. Previous studies in African-Americans reported African ancestry to be associated with decreased TG, whereas the association between African ancestry and LDL-C and HDL-C has been inconsistent [25]. However, the previous studies were conducted in African-Americans, who have been shown to have a high degree of non-African ancestry (~18.5%) [10]. We found a strong association between non-African ancestry and serum TG despite its very low proportion (3%) in this population. Our finding suggests that in African ancestry populations, genetic factors are likely a significant determinant of fasting TG levels, but not of fasting LDL-C, HDL-C, TG/HDL-C ratio, or non-HDL-C. Much of the inter-individual variation in serum TGs in African ancestry populations is unexplained. Genome-wide association studies have identified a number of loci associated with serum TGs but it is unclear if these loci are causally related and they explain only a small fraction of the genetic contribution to TG in African ancestry populations [26]. Further studies are needed to identify the loci that control TG levels in African ancestry individuals.

We observed that older age is associated with lower TG and TG/HDL-C ratio, and greater HDL-C levels, but not with LDL-C and nonHDL-C. In general, in men, TG levels increase up to age of 50 years and decline thereafter, and our findings are consistent with previous reports [27]. The decline in TG with aging is thought to be due to increased conversion of VLDL to LDL particles and decreased clearance and catabolism of VLDL and LDL

particles due to reduced expression of LDL receptors and activity of lipoprotein lipase [28]. However, the association with older age and HDL-C levels less clear [29, 30]. Increased HDL-C levels observed in older men in some studies may be due to decreased levels of androgens in men with aging [30], or the fact that higher HDL-C levels may be related to longevity [29].

Fasting serum measures of diabetes and insulin resistance were positively and independently associated with serum TG, TG/HDL-C ratio and nonHDL-C, and inversely associated with HDL-C in our study. Glucose and insulin abnormalities are often only weakly associated with TG and HDL-C in African-Americans [31]. The mechanisms underlying this observation are unclear, but suggest that African ancestry individuals may be more resistant to the dyslipidemic effects of T2DM. The TG/HDL-C ratio has been reported to be closely related to insulin resistance [32], although conflicting findings have been reported in studies of African-Americans [31, 33]. In our study HOMA-IR was a significant, independent correlate of TG/HDL-C ratio, a finding which provides additional evidence that the TG/HDL-C ratio may be associated with insulin resistance regardless of ethnicity. The inconsistency of findings among populations of African ancestry could be due to the small sample size in some of the previous studies, or because of the differences in the prevalence of general obesity across previous studies in populations of African ancestry. Indeed, Li et al. reported that the association between TG/HDL-C ratio and hyperinsulinemia is stronger among lean individuals [33] than among obese, regardless of their ethnicity. It is possible that TG/HDL-C ratio is associated with insulin resistance in our Afro-Caribbean male population, and in previous study of East Africans [34], but not in African-Americans, because of low levels of total body fat in our Afro-Caribbean population, as well as in East Africans.

Diastolic blood pressure, but not systolic blood pressure, was positively associated with TG, TG/HDL-C ratio, nonHDL-C and LDL-C levels in our study. Dyslipidemia is reported in more than half of hypertensive patients [35]. Some studies report a positive association between hypertension and TG and LDL-C, but not with HDL-C [36]. The relationship between hypertension and lipoprotein levels may be due to the toxic effects of triglyceride-rich lipoproteins and LDL-C on the vascular endothelium, which leads to increased peripheral vascular resistance [37].

We found an independent association between physical activity and alcohol intake with HDL-C. Regular participation in physical activity has been shown to positively alter HDL-C metabolism by increasing the production and action of several enzymes that function to enhance the reverse cholesterol transport system [38]. Similar to our findings, others have shown that light to moderate alcohol consumption has beneficial effects on HDL-C [39], although the precise mechanisms are only partly understood. Some have suggested that moderate consumption of alcohol increases HDL-C by increasing the transport rates and of ApoA-I and ApoA-II [40].

Although, previous studies have shown that independent of overall adiposity, greater skeletal muscle adipose tissue infiltration and/or lower subcutaneous adipose tissue around skeletal muscle are associated with glucose abnormalities, insulin resistance, and T2DM [7],

to our best knowledge, no previous studies have focused on the relationship of skeletal muscle adiposity with the TG/HDL-C ratio, a marker of insulin resistance. The question of whether lower adiposity in the subcutaneous depot or greater adiposity within skeletal muscle leads to insulin resistance remains to be clarified, and thus, it is important to emphasize that in our study, subcutaneous AT, but not skeletal muscle AT infiltration, was inversely and independently associated with the TG/HDL-C ratio. As mentioned previously, some have hypothesized that in addition to impaired lipid storage and utilization, an overflow of AT storage in the inter- and intra- muscular compartments may be due to a defect in the ability of subcutaneous AT to store excess fatty acids [20]. We have additionally confirmed the findings from a number of previous studies [7], and found that men with T2DM have greater skeletal muscle AT infiltration and less subcutaneous AT than non-diabetic men, independent of differences in age, body size, total body fat or skeletal muscle area. However, a causal link between skeletal muscle adiposity and T2DM remains to be established in large, well-designed longitudinal studies.

The present study has several limitations. First, our study was cross-sectional in design and our analyses may be subject to cohort effects and biases introduced by selective survivorship, and thus it limits our ability to establish temporal relationships with serum lipid and lipoprotein levels. Second, information collected by questionnaires depends on participants' recall and this may have limited our ability to detect relationships with some variables. Third, it is possible that individuals who have a relatively large subcutaneous AT area in their calves, also store a relatively larger proportion of abdominal AT in the subcutaneous compartment, and not in the visceral or liver depot. Unfortunately, visceral AT and ectopic liver AT infiltration were not assessed in our study, and thus, we were not able to test if the observed associations are independent of these AT depots. However, in the multivariable model with waist circumference, the association between calf subcutaneous AT and TG levels remained significant ($P < 0.05$, data not shown). Fourth, diet and exercise, important determinants of lipids, lipoproteins and adiposity, were not directly assessed in our study. Fifth, there are likely differences in cultures and the degree of westernization between the Afro-Caribbeans, sub-Saharan Africans, and African-Americans, and future studies should include populations of African ancestry living outside of the Caribbean region. Finally, by obtaining a single CT slice of the calf muscle, we were able to measure a relatively small depot of skeletal muscle AT [11].

In conclusion, our study illuminates a novel relationship of serum lipid and lipoprotein levels with ectopic skeletal muscle AT infiltration and subcutaneous AT, independent of total and central adiposity. Our findings also confirm a likely important role of genetic factors in the determination of ethnic differences in serum TG levels. Nonetheless, much of the variation in serum lipid and lipoprotein levels remained unexplained and highlights the need for further studies to better understand the determinants of lower TG and higher HDL-C levels in African ancestry men.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

General characteristics and age-adjusted correlates of serum lipid and lipoprotein levels in Afro-Caribbean men (N=1821)

| Characteristics | Mean (\pm SD) or % (N) | Unit | Triglycerides | LDL-C | HDL-C |
|---|------------------------------|--------|---|-----------------------------------|----------------------------------|
| | | | Age-adjusted absolute difference in lipoprotein levels per SD or unit (95%CI) | | |
| Age (years) | 58.9 \pm 10.3 | 10.3 | -0.42 (-0.90,0.05) | 0.66 (-1.18,2.50) | 1.40 (0.81,2.00) ^b |
| Non-African Genetic Ancestry (%) | 3.1 (55) | 1 | 4.15 (1.37,6.93) ^a | 0.62 (-10.15,11.4) | -1.03 (-4.50,2.43) |
| BMI (kg/m ²) | 27.5 \pm 6.4 | 6.4 | 1.91 (1.45,2.38) ^a | 4.44 (2.6,6.27) ^b | -3.01 (-3.59,-2.43) ^b |
| Waist Circumference (cm) | 92.8 \pm 11.5 | 11.5 | 3.30 (2.85,3.76) ^b | 6.54 (4.71,8.36) ^b | -4.29 (-4.85,-3.73) ^b |
| Total Body Fat (%) | 20.8 \pm 5.9 | 5.9 | 3.46 (3.00,3.92) ^b | 8.45 (6.61,10.29) ^b | -4.15 (-4.73,-3.58) ^b |
| Calf Total Adipose Tissue Area (mm ²) | 1822.2 \pm 810.1 | 810.1 | 1.67 (1.20,2.14) ^b | 4.55 (2.72,6.38) ^b | -2.93 (-3.51,-2.35) ^b |
| Calf Subcutaneous Adipose Tissue Area(mm ²) | 1364.5 \pm 677.7 | 677.7 | 1.90 (1.43,2.37) ^b | 6.07 (4.23,7.91) ^b | -3.01 (-3.59,-2.42) ^b |
| Calf Intermuscular Adipose Tissue Area (mm ²) | 294.6 \pm 323.5 | 323.5 | 0.28 (-0.22,0.77) | -0.44 (-2.35,1.48) | -1.36 (-1.97,-0.74) ^b |
| Calf Muscle Area (mm ²) | 7488.2 \pm 1330.8 | 1330.8 | 1.08 (0.56,1.59) ^b | 2.12 (0.12,4.13) ^a | -2.18 (-2.82,-1.54) ^b |
| Calf Muscle Density (mg/cm ³) | 76.5 \pm 3.6 | 3.6 | -0.35 (-0.87,0.17) | 1.87 (-0.12,3.87) | 1.38 (0.74,2.02) ^b |
| Fasting Glucose (mg/dL) | 104.1 \pm 35.2 | 35.2 | 1.71 (1.23,2.19) ^b | 2.36 (0.49,4.23) ^a | -1.09 (-1.69,-0.49) ^b |
| Fasting Insulin (mg/dL) | 12.2 \pm 6.8 | 6.5 | 3.00 (2.53,3.47) ^b | 4.33 (2.46,6.19) ^b | -3.13 (-3.72,-2.54) ^b |
| HOMA-IR | 3.2 \pm 2.2 | 2.2 | 3.15 (2.69,3.61) ^a | 4.22 (2.36,6.07) ^b | -2.83 (-3.42,-2.24) ^b |
| Systolic Blood Pressure (mmHg) | 138.5 \pm 23.0 | 23.0 | 1.76 (1.27,2.24) ^b | 3.72 (1.82,5.62) ^b | -0.52 (-1.13,0.10) |
| Diastolic Blood Pressure (mmHg) | 81.0 \pm 12.9 | 12.9 | 1.98 (1.51,2.44) ^b | 4.27 (2.44,6.10) ^b | -0.39 (-0.98,0.20) |
| Walked >3 times per week (%) | 38.3 (698) | 1 | -1.34 (-2.32,-0.36) ^a | 0.13 (-3.66,3.92) | 2.49 (1.28,3.71) ^b |
| Currently Smoke (%) | 10.6 (193) | 1 | -1.04 (-2.59,0.52) | -7.63 (-13.63,-1.63) ^a | 2.97 (1.04,4.90) ^a |
| Alcohol Intake >3 drink per week (%) | 10.4 (190) | 1 | 0.60 (-0.96,2.17) | 0.80 (-5.24,6.85) | 6.55 (4.63,8.48) ^b |
| TV watching 14 hours per week (%) | 37.4 (681) | 1 | 1.42 (0.44,2.40) ^a | 4.32 (0.51,8.12) ^a | -0.21 (-1.44,1.02) |
| Caffeine intake (mg/day) | 92.9 \pm 77.4 | 77.4 | 0.75 (0.26,1.23) ^a | 1.37 (-0.51,3.25) | -0.22 (-0.82,0.39) |
| Obesity (%) | 24.4 (445) | 1 | 5.02 (3.93,6.11) ^b | 10.58 (6.29,14.86) ^b | -6.47 (-7.82,-5.11) ^b |

| Characteristics | Mean (\pm SD) or % (N) | Unit | Triglycerides | Age-adjusted absolute difference in lipoprotein levels per SD or unit (95%CI) | |
|--|------------------------------|------|--------------------------------------|--|----------------------------------|
| | | | | LDL-C | HDL-C |
| Type 2 Diabetes (%) | 20.5 (373) | 1 | 2.01 (0.81,3.21) ^a | 2.77 (-1.88,7.42) | -2.54 (-4.04,-1.05) ^b |
| Hypertension (%) | 48.7 (887) | 1 | 3.85 (2.88,4.82) ^b | 6.65 (2.86,10.44) ^b | -2.09 (-3.31,-0.87) ^b |
| Currently taking hypoglycemic drugs or insulin (%) | 14.9 (268) | 1 | -0.28 (-1.65,1.10) | -0.65 (-5.98,4.69) | -2.26 (-3.98,-0.55) ^a |
| Currently taking lipid-lowering drugs (%) | 3.9 (66) | 1 | 4.05 (1.49,6.61) ^a | 15.75 (5.86,25.64) ^a | -3.04 (-6.22,0.14) |
| Currently taking anti-hypertensive drugs (%) | 23.2 (396) | 1 | 2.90 (1.71,4.09) ^b | 7.02 (2.35,11.69) ^a | -3.35 (-4.84,-1.86) ^b |

BOLD indicates significance at $p < 0.10$ to be tested in multivariable model

^a $P < 0.05$

^b $P < 0.0001$

Table 2

Correlates of serum lipid and lipoprotein levels in multivariable models in Afro-Caribbean men (N=1821)

| Variable | Unit | Absolute difference per SD or unit (95%CI) | | |
|--|-------|--|--|--|
| | | Triglycerides | LDL-C | HDL-C |
| Age (yrs) | 10.3 | -1.03 (-1.52, -0.53) ^b | 0.97 (-0.98, 2.93) | 1.60 (1.01, 2.18) ^b |
| Non-African Genetic Ancestry (y/n) | 1 | 3.48 (0.85, 6.11) ^a | | |
| Waist (cm) | 11.5 | | | -3.80 (-4.45, -3.14) ^b |
| Total Body Fat (%) | 5.9 | 2.82 (2.06, 3.57) ^b | 9.76 (7.71, 11.82) ^b | |
| Calf Subcutaneous adipose tissue Area (mm ²) | 677.7 | -0.75 (-1.44, -0.06) ^a | | |
| Calf Muscle Density (mg/cm ³) | 3.6 | | 5.46 (3.39, 7.54) ^b | |
| Glucose (mg/dL) | 35.2 | 1.21 (0.74, 1.68) ^b | | |
| Insulin (mg/dL) | 6.5 | 1.73 (1.22, 2.24) ^b | | -1.36 (-2.00, -0.72) ^b |
| Systolic Blood Pressure (mmHg) | 23.0 | | | -0.52 (-0.08, 1.13) |
| Diastolic Blood Pressure (mmHg) | 12.9 | 1.05 (0.59, 1.51) ^b | 2.28 (0.40, 4.16) ^a | |
| Walked >3 times per week (y/n) | 1 | | | 1.37 (0.20, 2.53) ^a |
| Alcohol Intake >3 drink per week (y/n) | 1 | | | 6.74 (4.89, 8.60) ^b |
| TV watching 14 hours per week (y/n) | 1 | | 3.46 (-0.34, 7.26) | |
| R² | | 0.17 | 0.06 | 0.16 |

Variables entered in multivariable model had P<0.10 in age-adjusted analyses. All covariates with P<0.10

(**BOLD**) in multivariable models are shown. Age was forced into each model.

R²: percent of variation in lipid and lipoprotein levels explained collectively by significant variables.

^aP<0.05

^bP<0.001