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Markers of Inflammation Are Heritable and Associated with Subcutaneous and Ectopic Skeletal Muscle Adiposity in African Ancestry Families

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Abstract

Background: Skeletal muscle adipose tissue (AT) infiltration, or myosteatosis, appears to be greater in African compared with European ancestry individuals and may play a role in type 2 diabetes mellitus (T2DM), a disease that disproportionally affects African ancestry populations. Inflammation is one mechanism that may link myosteatosis with increased T2DM risk, but studies examining the relationship between inflammation and myosteatosis are lacking.

Methods: To examine these associations, we measured skeletal muscle subcutaneous AT, intermuscular AT, and skeletal muscle density using quantitative computed tomography and serum markers of inflammation in 471 individuals from 8 Afro-Caribbean multigenerational families [mean family size 67; mean age 43 years; mean body mass index (BMI) 28 kg/m^2].

Results: After removing the variation attributable to significant covariates, heritabilities of inflammation markers [C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α)] ranged from 33% (TNFα) to 40% (CRP); all $P < 0.01$. Higher CRP, IL-6, and TNF-α were associated with lower subcutaneous AT around skeletal muscle ($r = -0.13$ to -0.19, $P < 0.05$). Higher CRP was additionally associated with lower skeletal muscle density, indicative of greater intramuscular AT ($r = -0.10$, $P < 0.05$), hyperinsulinemia ($r = 0.12$, $P < 0.05$), and increased homeostasis model assessment of insulin resistance (HOMA-IR) ($r = 0.17$, $P < 0.01$).

Conclusions: Our findings suggest that heredity may play a significant role in the determination of several markers of inflammation in African ancestry individuals. Higher concentrations of CRP appear to be associated with greater skeletal muscle AT infiltration, lower subcutaneous AT, hyperinsulinemia, and insulin resistance. Longitudinal studies are needed to further evaluate the relationship between inflammation with changes in skeletal muscle AT distribution with aging and the incidence of T2DM.

Introduction

Obesity, insulin resistance, and type 2 diabetes mellitus (T2DM) are more common in individuals of African ancestry than other ethnic groups.[1–8] Although, there is a strong association between obesity and a greater production of a number of markers of inflammation,[9,10] some studies have suggested that regional body fat depots, such as visceral adiposity, may be more closely linked with certain markers of inflammation than general adiposity.[9,11,12] Emerging data suggest that ectopic skeletal muscle adipose tissue (AT) infiltration,[13,14] or myosteatosis,[15] is greater in men of African than of Caucasian ancestry at all levels of total adiposity, as well as among nonobese African ancestry men matched on age and total body fat.[14] Moreover, increased myosteatosis appears to be an important risk factor for T2DM, independent of total adiposity,[15] although the exact mechanisms linking myosteatosis and T2DM are still unclear. Increased accumulation of adipose tissue in the skeletal muscle could induce changes in muscle metabolism and insulin sensitivity via local secretion of inflammatory adipokines from adipose tissue cells surrounding muscle fibers.[16] However, studies examining the relationship between inflammation and myosteatosis are lacking, particularly in

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populations of African ancestry. Thus, the primary aim of the present study is to investigate potential associations between skeletal muscle adipose tissue infiltration and markers of inflammation, in particular, C-reactive protein (CRP), tumor necrosis factor-α (TNF-α), and interleukin-6 (IL-6) in multigenerational families of African ancestry.

Furthermore, the importance of heredity in determining inflammatory factors remains poorly defined in populations of African ancestry. In general, heritability of inflammatory markers was previously described mainly in nuclear families or sib-pair studies of African Americans, an African ancestry population with a high degree of non-African ancestry.[17,18] Thus, the use of our extended families with very little non-African ancestry should provide greater precision in heritability estimates. Therefore, the secondary aim of the present study is to determine the magnitude of genetic and environmental influences on markers of inflammation.

Methods

Study sample: The Tobago Family Health Study

The Tobago Family Health Study was designed to investigate the role of inheritance and environment in various components of body composition in African ancestry individuals. According to the 1990 census data based on self-report, the population of Tobago was 92% African descent, 4.5% mixed, 2% East Indian, 0.4% white, and 1% other.[19] We confirmed with ancestry informative markers that the Afro-Caribbean population of Tobago has a low level of non-African admixture (6%)[20] compared with the more genetically heterogeneous African-American population (17%–23.9%).[21–23] Probands for the Tobago Family Health Study were identified from an ongoing population-based prostate cancer screening study.[24] To be eligible, a proband had to be Afro-Caribbean, have had a spouse who was willing to participate in the study, and have at least six living offspring and/or siblings aged 18+ years who were residing in Tobago. Because we were interested in establishing a community-based sample of families, probands and their family members were recruited without regard to their health status. A total of 471 individuals aged 18–103 years (mean age 43 years) belonging to eight multigenerational families (mean family size 67 individuals) of West African ancestry were recruited. There are 357 parent–offspring, 465 full siblings, 92 grandparent–grandchildren, 1,087 avuncular, 85 half-sibs, and 1,360 cousins (3,446 relative pairs). At the time of analysis, fasting serum measurements of inflammatory and metabolic traits were available for 401 individuals belonging to seven pedigrees. Written informed consent was obtained from every participant, using forms and procedures approved by the Tobago Division of Health and Social Services and University of Pittsburgh Institutional Review Boards.

pQCT measures

A lower-leg peripheral quantitative computerized tomography (pQCT) scan was performed using the Stratec XCT-2000 device (Orthometrix, Inc., White Plains, NY) to evaluate the total, skeletal muscle, and adipose tissue cross-sectional areas of the calf. Scans were obtained at 66% of the tibial length, proximal to the terminal end of the tibia. This site was chosen because it is the region of the lower leg with the largest circumference of the calf with very little variability across individuals.[25] Different tissues in the analyses were separated according to different density thresholds, using the ''soft tissue'' algorithm. On the basis of the calibration, AT, muscle, and cortical bone were measured with mineral equivalent densities of 0, 80, and 1,200 mg/cm^3, respectively. Therefore, changes in muscle tissue to AT-like tissue would be detected as a shift in mineral equivalent density of the muscle from 80 to 0 mg/cm^3. Images of the cross-sectional area of skeletal muscle and adipose tissue and the density of skeletal muscle were analyzed using the Stratec analysis software (Version 5.5 D). To maintain consistency, all images were analyzed by a single investigator. The pQCT image was segmented into bone and soft tissue measures using edge detection and thresholding steps. We determined the calf cross-sectional area for total adipose tissue (TAT; mm^2), intermuscular adipose tissue (IMAT; mm^2; visible AT within the fascia surrounding skeletal muscle), and subcutaneous adipose tissue (SAT; mm^2). Skeletal muscle density was expressed in mg/cm^3 and is considered a valid measure of adipose tissue infiltration in skeletal muscle.[26] Muscle density reflects the skeletal muscle AT content such that greater AT infiltration within the muscle is associated with lower muscle density.

Dual-energy X-ray absorptiometry measures

Dual-energy X-ray absorptiometry (DXA) measurement of total body AT was made using a Hologic QDR 4500W densitometer (Hologic Inc., Bedford MA). Scans were analyzed with QDR software version 8.26a.

Inflammation and metabolic variables

All biochemical assays in fasting serum samples were performed in the Heinz Nutrition Laboratory at the University of Pittsburgh. CRP was measured turbidimetrically (Carolina Liquid Chemicals, Brea, CA); intra- and interassay coefficient of variation (CV) % was 5.5% and 3.0%, respectively. IL-6 was measured by ultrasensitive enzyme-linked immunosorbent assay (ELISA) (R&D Systems, Inc., Minneapolis, MN); intra- and interassay CV% was 8.4% and 9.3%, respectively. TNF-α was measured by an ultrasensitive ELISA (R&D Systems Inc.); inter- and intraassay CV% was 7.4% and 15.0%, respectively. Fasting serum glucose was measured using an enzymatic procedure; the CV% between runs was 1.8%. Insulin was measured using a radioimmunoassay (RIA) procedure developed by Linco Research, Inc.; the CV% between runs was 2.1%. The degree of insulin resistance was estimated by homeostasis model assessment (HOMA) according to the method described by Matthews et al.[27] In previous studies, HOMA has correlated reasonably well with insulin clamp techniques.[28]

Anthropometry, lifestyle, and medical conditions

Body weight was measured to the nearest 0.1 kg with participants wearing indoor clothing, but without shoes, using a balance beam scale. Standing height without shoes was measured to the nearest 0.1 cm using a wall-mounted stadiometer. Waist circumference was measured at the narrowest point of the waist using an inelastic fiberglass tape. Information on a wide range of lifestyle habits [current smoking (yes/no), current alcohol intake (more than one

drink per week (yes/no), walking (ever walked in the past week (yes/no)], history of medical conditions, medication use, and reproductive characteristics for women [age at menarche, post-menopausal status (yes/no), ever pregnant (yes/no), current oral contraceptive use (yes/no)] were assessed using standardized interviewer administered questionnaires. T2DM was defined as fasting serum glucose ≥ 126 mg/dL and/or currently taking antidiabetic medication. Impaired fasting glucose was defined as a fasting serum glucose level 100–125 mg/dL. Obesity was defined as BMI $\geq 30\,kg/m^2$.

Statistical analyses

Prior to analysis, the distributions of all continuous traits were first assessed for departures from normality, and, if necessary, transformation was performed to reduce skewness. CRP, IL-6, TNF-α, glucose, intermuscular adipose tissue, and skeletal muscle density were log transformed, whereas subcutaneous adipose tissue was square root transformed. To assess differences in measured variables in families between men and women, and between nondiabetics and diabetics, univariate regression analysis was performed (regress the variables of interest by gender and T2DM) using the variance components approach as implemented in SOLAR (Solar, Version 2.1.4; Southwest Foundation for Biomedical Research, San Antonio, TX[29]), which accounts for nonindependence among individuals. Adjusted Pearson correlation analyses using transformed variables were first performed by using SAS version 9.1 (SAS Institute, Cary, NC), ignoring the nonindependence of the subjects within each family. However, we subsequently performed the same analysis limited to the 86 unrelated individuals (78 married-in plus 8 founders from pedigrees). Correlation coefficients were compared between these two analyses and found to be similar. Thus, we present the correlation coefficients for the entire dataset. All correlation analyses were adjusted for anti-inflammatory medication use. Because of their presumed relationships with the components of skeletal muscle composition traits, and our interest in relationships independent of total adiposity, age, gender, height, and DXA total body adipose tissue were evaluated as covariates. Residual heritability (h2r) and the effects of all potentially significant covariates measured in our study (age, gender, total body adipose tissue, current smoking, current alcohol intake, minutes walking per week, postmenopausal status, parity, age at menarche, oral contraceptive use) were estimated by quantitative genetic methods using SOLAR. We required $P \leq 0.05$ for inclusion in our final model for each trait. Additionally, we assessed the potential for pleiotropic genetic effects acting on inflammatory markers and skeletal muscle ectopic fat depots by estimating genetic correlation (ρ_G) and environmental correlation (ρ_E) using a bivariate extension of the variance components framework in SOLAR.[30]

Results

Mean age of the 187 men and 284 women was 43 years and ranged from 18 to 103 years (Table 1). Participants were predominantly women (60.3%) and moderately overweight [body mass index (BMI) $28.3\,kg/m^2$]. Only 3% of study participants used anti-inflammatory drugs regularly and 6.7% used antidiabetic drugs regularly. No participant used oral corticosteroids. More men than women smoked (11.4 vs. 2.5%) and drank alcohol (29.6 vs. 2.5%) on a regular basis. Approximately one third of the women were postmenopausal and one third used oral contraceptives. More than two thirds of the women were pregnant at least once in their life. BMI and total body AT percent were significantly greater in women compared with men, but waist circumference was similar between genders. Prevalence of obesity was greater in women compared to men (43% vs. 20%), but rates of T2DM and impaired fasting glucose were similar.

We tested for gender differences in skeletal muscle composition and markers of inflammation and T2DM (Table 1). Independent of differences in age and height, women had more total AT, but less skeletal muscle in the calf than men ($P < 0.001$). Women had more subcutaneous AT, but also more skeletal muscle AT infiltration, as indicated by more intermuscular AT and less dense skeletal muscle (all $P < 0.005$), independent of total body adiposity and skeletal muscle area. Compared to men, women also had greater concentrations of CRP, IL-6, insulin, and a higher HOMA index (all $P \leq 0.05$), independent of total body adiposity.

CRP and IL-6 were positively associated with age (Table 2; $P < 0.05$). CRP and IL-6 were also positively correlated with BMI, waist circumference, and DXA total body AT (all $P < 0.05$), with CRP demonstrating a stronger correlation than IL-6. All inflammation markers were inversely associated with subcutaneous AT ($P < 0.05$), although only CRP was positively associated with total AT in the calf ($P < 0.01$). Additionally, higher CRP was associated with lower skeletal muscle density ($P < 0.01$), higher insulin levels ($P < 0.05$), and increased insulin resistance as measured by the HOMA index ($P < 0.01$). Correlations coefficients remained similar after excluding individuals with T2DM (data not shown).

Residual heritability (h2r), the proportion of variance due to additive genetic effects, was estimated for inflammation markers after removing the variation attributable to significant covariates (Table 3). Heritabilities of inflammation markers ranged from 33% (TNF-α) to 40% (CRP) (all $P < 0.01$). Significant demographic, lifestyle, anthropometric, and reproductive factors (Table 3) accounted for less than 1% (TNF-α) to 22% (CRP) of the total phenotypic variation in the inflammation markers. We have also estimated heritability of subcutaneous and ectopic skeletal muscle adiposity traits. After removing the variation attributable to all significant covariates measured in our study, which explained 31%–70% of the total phenotypic variation in skeletal muscle adiposity traits, all three traits were significantly heritable, with the heritability values ranging from 33% (intermuscular AT) to 43% (subcutaneous AT) (Table 3). Finally, considering the fact that phenotypic correlation between inflammation markers and subcutaneous fat, and to some extent ectopic AT adiposity, was significant, and that these traits were heritable, we tested if a common set of genes might influence inflammation markers and subcutaneous and ectopic skeletal muscle adiposity traits. However, no significant genetic correlations were found between inflammation markers and subcutaneous and ectopic skeletal muscle adiposity (data not shown).

Discussion

The current analysis examined the interrelationships among adipose tissue depots and markers of inflammation in large, multigenerational families of African ancestry, with a

Table 1. Characteristics of Tobago Family Study Participants: Total and Comparisons Between Genders

Characteristics	*Total* (n=*471*)	*Men* (n=*187*)	*Women* (n=*284*)	*Unadjusted* P *value*	*Adjusted* P *value*
Age (years)	42.7±0.8	42.7±1.2	42.7±1.0	0.99	N.A.
Lifestyle factors					
Alcohol use (%)	13.2%	29.6%	2.5%	**<0.001**	**<0.001**
Current smoking (%)	4.9	11.4	0.7	**<0.001**	**<0.001**
Walked in the past week (%)	69.9%	73.1%	67.8%	0.22	0.76
Reproductive traits					
Oral contraceptives (%)	N.A.	N.A.	32.9%	N.A.	N.A.
Everp (%)	N.A.	N.A.	77.1%	N.A.	N.A.
Postmenopausal status (%)	N.A.	N.A.	31.9%	N.A.	N.A.
Anthropometrics and calf muscle composition					
BMI (kg/m^2)[a]	28.3±6.4	26.3±4.6	28.5±6.3	**<0.001**	**<0.001**
Waist (cm)[a]	89.9±15.4	90.3±11.7	88.3±16.8	0.83	0.84
DXA total body adipose tissue (%)[b]	28.7±10.9	18.6±6.3	35.4±7.7	**<0.001**	**<0.001**
Total adipose tissue (mm^2)[b]	2500±1224	1655±790	3072±1131	**0.35**	**0.35**
Subcutaneous adipose tissue (mm^2)[c]	2172±1168	1341±712	2734±1079	**<0.001**	**<0.001**
Intramuscular adipose tissue (mm^2)[c]	202±269	169±204	225±304	0.48	**0.005**
Muscle Density (mg/cm^3)[d]	73.7±5.0	75.4±4.1	72.4±5.2	**<0.001**	**0.016**
Muscle Area (mm^2)[b]	6640±1226	7415±1121	6116±996	**<0.001**	**<0.001**
Markers of inflammation and type 2 diabetes mellitus*					
CRP (mg/L)[e]	2.1±2.8	1.5±2.1	2.5±3.1	**0.00015**	**0.009**
IL-6 (pg/mL)[e]	2.7±2.2	2.3±1.6	3.0±2.5	**0.0001**	**0.011**
TNF-α (pg/mL)[e]	2.4±2.3	2.3±2.1	2.5±2.5	0.17	0.43
Glucose (mg/dl)[f]	87.5±29.1	84.7±22	89.4±33.1	0.18	0.12
Insulin (μU/ml)[f]	15.1±9.8	13.5±7.4	16.9±10.9	**0.0008**	**<0.001**
HOMA[f]	3.6±2.7	3.0±1.8	3.9±3.1	**0.0009**	**0.05**
Medical conditions and medication use					
Obesity (%)	33.9%	20.0%	43.1%	**<0.001**	—
T2DM (%)	9.9%	7.6%	11.4%	0.22	—
Impaired fasting glucose (%)	9.1%	7.7%	10.1%	0.42	—
Anti-inflammatory drugs (%)	3%	1.6%	3.9%	0.15	—
Antidiabetic drugs (%)	6.7%	4.7%	8.1%	0.16	—

Data are presented as unadjusted means±standard deviation (SD).
[a]Adjusted for age.
[b]Adjusted for age and height.
[c]Adjusted for age, height, and DXA total body adipose tissue.
[d]Adjusted for age, height, DXA total body adipose tissue, and pQCT muscle area.
[e]Adjusted for age, DXA total body adipose tissue, and current anti-inflammatory medication use.
[f]Adjusted for age, DXA total body adipose tissue, and current antidiabetic medication use.
*Data available for 401 individuals.
BMI, body mass index; DXA, dual-energy X-ray absorptiometry; CRP, C-reactive protein; IL-6, interleukin-6; TNF-α, tumor necrosis factor-α; HOMA, homestasis model assessment; T2DM, type 2 diabetes mellitus.

special focus on the distribution of skeletal muscle adipose tissue. Our findings suggest that greater concentrations of CRP are correlated with less subcutaneous adipose tissue around skeletal muscle and greater adipose tissue infiltration in skeletal muscle, but also with hyperinsulinemia and insulin resistance, independent of total body adiposity. We additionally defined the contribution of heredity to the markers of inflammation and found that heredity plays a significant role in the determination of several markers of inflammation in these families of African ancestry.

Similar to the findings from our study, a positive association between myosteatosis and CRP was previously described in 20 healthy elderly white men undergoing elective vertebral surgery.[31] A recent report of 2,651 white and African-American old men and women, aged 70–79 years[32] found that myosteatosis was associated with increased IL-6 in men of all ethnicities, with increased IL-6, CRP, and TNF-α in white women, but with increased CRP only in African-American men. Although the findings of their study suggested a trend toward a link between lower inflammatory markers and higher subcutaneous adipose tissue around skeletal muscle, the results were inconsistent.[32] To our knowledge, ours is the first study to report an inverse significant association between markers of inflammation and subcutaneous adipose tissue in the leg.

Our findings have a potential clinical importance, because previous studies have shown that independent of overall adiposity, greater skeletal muscle adipose tissue infiltration, and lower subcutaneous adipose tissue around skeletal muscle are associated with glucose abnormalities, insulin resistance, and T2DM.[15] However, the question of whether lower adiposity in the subcutaneous depot or greater adiposity within skeletal muscle leads to impaired glucose tolerance and insulin resistance remains to be clarified. Some have hypothesized that in addition to impaired lipid storage and utilization, an overflow of AT storage in the inter- and intramuscular compartments may be due to a defect in the ability of subcutaneous AT to store excess fatty acids.[33] All

Table 2. Pearson Correlations with Inflammation Markers

	CRP (mg/L)	*IL-6 (pg/mL)*	*TNF-α (pg/mL)*
Age[a] (years)	**0.20*** **	**0.12***	0.01
BMI (kg/m^2)[b]	**0.39*** **	**0.20*** **	**0.11***
Waist circumference (cm)[b]	**0.37*** **	**0.20*** **	0.07
DXA total dody adipose tissue (%)[c]	**0.38*** **	**0.20*** **	0.10
Total adipose tissue (mm^2)[c]	**0.16****	0.03	0.02
Skeletal muscle area (mm^2)[c]	**0.14***	−0.06	0.001
Subcutaneous adipose tissue (mm^2)[d]	**−0.14****	**−0.19*** **	**−0.13***
Intermuscular adipose tissue (mm^2)[d]	−0.003	−0.04	0.07
Skeletal muscle density (mg/cm^3)[e]	**−0.10***	−0.05	−0.09
Glucose (mg/dL)[f]	0.10	−0.07	0.04
Insulin (μU/mL)[f]	**0.12***	0.04	0.05
HOMA[f]	**0.17****	0.03	0.07

Significant correlations are presented in bold.
HOMA (glucose/insulin index) indicates insulin resistance.
[a]Adjusted for gender and current anti-inflammatory medication use.
[b]Adjusted for age, gender and current anti-inflammatory medication use.
[c]Adjusted for age, gender, height and current anti-inflammatory medication use.
[d]Adjusted for age, gender, height, DXA total body adipose tissue %, and current anti-inflammatory medication use.
[e]Adjusted for age, gender, height, DXA total body adipose tissue %, skeletal muscle area, and current anti-inflammatory medication use.
[f]Adjusted for age, gender, DXA total body adipose tissue %, current anti-inflammatory medication use, and current antidiabetic treatment.
*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.
CRP, C-reactive protein; IL-6, interleukin-6; TNF-α, tumor necrosis factor-α; BMI, body mass index; DXA, dual-energy X-ray absorptiometry; HOMA, homeostasis model assessment.

previous studies have been cross sectional, and a causal link of myosteatosis and/or subcutaneous adipose tissue with T2DM remains to be established in longitudinal studies. Our findings indicate that such longitudinal studies in African ancestry populations should additionally include CRP and possibly other inflammatory markers to test for the causal relationships between inflammation, skeletal muscle adiposity, and the development of T2DM.

There is some evidence that adipose tissue isolated from specific fat depots, such as visceral adipose tissue, may express higher levels of inflammatory markers,[34] but such experiments still remain to be conducted for adipose tissue isolated from skeletal muscle and subcutaneous adipose tissue depots. CRP is released mainly from the liver after stimulation by high circulating concentrations of IL-6 and TNF-α.[35] CRP has been previously related to ectopic adipose tissue infiltration in the liver and with visceral AT accumulation in Japanese T2DM patients,[35] but no such studies have been conducted in other ethnic groups. Thus, future studies should also include measures of hepatic adipose tissue infiltration because it is possible that the observed association between CRP and myosteatosis may be driven by increased ectopic adipose tissue infiltration in the liver.

Aging is accompanied by a two- to four-fold increase in serum levels of proinflammatory markers, including CRP, IL-6, and TNF-α.[36] We confirmed a positive association between age and CRP and IL-6, even in this relatively young sample of African ancestry individuals. Several large cohort studies[37–39] have also shown that compared with other ethnic groups African ancestry individuals have significantly higher CRP levels. Data on ethnic differences in IL-6 and TNF-α are more limited. Some studies found higher concentrations of IL-6,[40] but similar levels of TNF-α[41] in individuals of African compared with European ancestry. Our study only focused on African ancestry individuals, and it is not possible to compare our values with these other studies due to assay differences and differences in cohort characteristics.

Table 3. Heritability of Inflammation Markers and Subcutaneous and Ectopic Skeletal Muscle Adiposity

Phenotype	*h2r*[a] ± *SE*	R^{2} [b]	*Significant covariates*
CRP (mg/L)	0.40 ± 0.12[c]	0.22	Sex, total body fat %, alcohol intake, menopause
IL-6 (pg/mL)	0.39 ± 0.10[c]	0.08	Total body fat %, smoking
TNF-α (pg/mL)	0.33 ± 0.11[c]	< 0.01	Oral contraceptive use
Subcutaneous adipose tissue (mm^2)	0.42 ± 0.10[c]	0.70	Age, total body fat %, smoking, ever pregnant
Intermuscular adipose tissue (mm^2)	0.33 ± 0.11[c]	0.32	Age, sex, total body fat %, smoking, alcohol intake, ever pregnant
Skeletal muscle density (mg/cm^3)	0.35 ± 0.09[c]	0.31	Age, total body fat %

We tested for age, gender, total body adipose tissue percent, current smoking, current alcohol intake, minutes walking per week, postmenopausal status, pregnancy history (ever pregnant), age at menarche, oral contraceptive use [+current anti-inflammatory medication use for inflammation markers (NSAID)].
[a]Proportion of variance due to residual additive genetic effects (residual heritability, h2r).
[b]Proportion of variance explained by all significant measured covariates.
[c]$P < 0.01$.
CRP, C-reactive protein; IL-6, interleukin-6; TNF-α, tumor necrosis factor-α.

Previous studies have found CRP concentrations to be higher in premenopausal women than in men across different ethnicities, possibly because of estrogenic effects on CRP levels.[42] In contrast, IL-6 and TNF-α concentrations have been reported to be lower in women than in men.[43] Data on gender differences in IL-6 and TNF-α among younger and middle-aged individuals are sparse. In our study, women had greater levels of CRP and IL-6 than men, which may be due to the large proportion of premenopausal women and significantly greater prevalence of obesity among women compared with men.

Our analyses also provide evidence of a moderate genetic influence on markers of inflammation. To our knowledge, this is the first report that heredity may play an important role in the regulation of IL-6 concentrations among individuals of African ancestry. Heritability of CRP in African Americans from the Jackson Heart Family Study was 45%, similar to our estimate of 40%.[17] In contrast, another study did not find CRP levels to be significantly heritable in African Americans.[18] To our knowledge, the heritability of TNF-α among individuals of African ancestry has only been estimated in one study and was considerably higher than in the current sample of families (68%).[44] However, that study was conducted among Ugandan pedigrees that had a high prevalence of tuberculosis, whereas our families were recruited without regard to their health status. After adjusting for age and total body adiposity, no significant genetic correlation was observed between markers of inflammation and subcutaneous and ectopic skeletal muscle adiposity. Thus, although subcutaneous adipose tissue was associated with markers of inflammation in our study, our findings suggest that the genetic basis for inflammation likely involves different etiological pathways.

There are several potential limitations of our study. The relatively small sample size may have influenced our heritability estimates. However, extended multigenerational families provide greater precision in heritability estimates than nuclear families or sib-pairs, the sampling unit of the vast majority of previous studies. In addition, heritability estimates do not provide insight on the number of loci that contribute to a trait or their magnitude of effect, and additional studies are needed to define the specific allelic variants that contribute to inflammation markers and skeletal muscle adiposity traits. The heritability estimates are relatively conservative because they do not count the genetic effects caused by gene–environment interactions. Our study was cross sectional and cannot delineate the temporal relationships between inflammation and myosteatosis. Furthermore, specific foods and overall dietary patterns may be associated with markers of inflammation, but the data on dietary intake and dietary patterns were not collected in our study. Another limitation of our study is the lack of data on chronic infections, such as pulmonary tuberculosis or helminth infections, which have been reported to be positively correlated with CRP levels. Additionally, by obtaining a single slice in the calf muscle, we were able to only measure a relatively small depot of skeletal muscle AT.[26] Nevertheless, a single image is commonly used as a proxy measure of whole body skeletal muscle,[45] and previous studies have noted a relatively strong correlation between AT infiltration in the calf and larger skeletal muscle groups such as the thigh.[46]

In conclusion, higher concentrations of CRP appear to be related to myosteatosis. Our findings also suggest that heredity has a significant impact on several markers of inflammation in African ancestry individuals. It is still a matter of debate as to whether insulin resistance and inflammation cause grater myosteatosis or whether excessive myosteatosis causes insulin resistance and inflammation. Longitudinal studies are needed to further evaluate the relationship between inflammation with changes in skeletal muscle adipose tissue distribution with aging and the incidence of T2DM.

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Author Disclosure Statement

The authors have nothing to disclose.

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