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Sex and genetic effects on upper and lower body fat and associations with diabetes in multigenerational families of African heritage

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Abstract

Very few studies have comprehensively defined the genetic and environmental influences on body fat storage in the arms and legs and their association with diabetes, especially in families of African heritage. We analyzed body fat distribution by dual-energy x-ray absorptiometry (percentage total fat, percentage trunk fat, percentage arm fat, and percentage leg fat) and fasting serum glucose in 471 individuals (mean age, 43 years) from 8 multigenerational Afro-Caribbean families (mean family size = 51; 3535 relative pairs). Diabetes was inversely associated with percentage leg fat ($P = .009$) and, to some extent, positively associated with percentage arm fat independent of age, sex, and body size ($P = .08$), but not with anthropometric or dual-energy x-ray absorptiometric measures of total and central adiposity. Furthermore, percentage leg fat was inversely, whereas percentage arm fat was positively, associated with body mass index, waist circumference, and serum glucose ($P < .01$). Residual heritability (h2r) for arm and leg fat was significant ($P < .01$) and high: 62% (for percentage arm fat) and 40% (for percentage leg fat). Moreover, sex-specific h2r for leg fat was considerably higher ($P = .02$) in women than in men (h2r values, 58% vs 17%, respectively). Genetic correlation (ρ_G) between arm and leg fat was −0.61 ($P < .01$), suggesting that only 37% of the covariation between these 2 adipose tissue depots may be due to shared genetic influences. This study provides new evidence for a strong genetic and sex contribution to upper and lower body fat, with relatively little covariation between these traits due to shared genes. Our findings also suggest that, in this population, leg fat is associated with diabetes independent of overall adiposity.

1. Introduction

Obesity is strongly associated with type 2 diabetes mellitus, and both disorders disproportionately affect individuals of African descent. Although the association between body mass index (BMI) and type 2 diabetes mellitus is well established [1,2], epidemiologic evidence suggests that the association of diabetes with central obesity is even stronger than the association with total obesity [3-7]. However, BMI and waist circumference, the most widely used measures of obesity, do not account for the variation in body fat distribution, which can considerably differ for the same BMI [8] and across different sex [9], age [10], and ethnic groups [11,12]. The increased prevalence of diabetes among individuals of African origin cannot be explained simply by differences in total and central adiposity as measured by BMI, total body fat, or waist circumference [13,14]. Even nonobese individuals of African origin have higher levels of fasting glucose and are more insulin resistant compared with other ethnic groups [13,14]. It is possible that ethnic differences in regional body fat distribution contribute to ethnic differences in risk of diabetes.

Only a few studies to date have focused on peripheral accumulation of body fat. These studies have revealed that

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leg fat is associated with more favorable glucose concentrations, even after accounting for overall and abdominal fat [15-18]. However, the association of fat depots in the upper extremities with diabetes, as well as the importance of heredity in determining body fat distribution in the arms and legs, remains unknown, especially in populations of African ancestry. Thus, the aim of the present study was to investigate the influence of genetic and environmental factors on dual-energy x-ray absorptiometry (DXA)–measured body fat distribution in the upper and lower body and to explore their associations with diabetes in a unique sample of large, multigenerational families of African heritage.

2. Methods

In 2003, we began The Tobago Family Health Study to better understand the role of heredity and lifestyle in the regulation of body composition. To date, we have recruited 471 individuals, without regard to their health status, aged 18 to 103 years (mean age, 43 years) belonging to 8 multigenerational families (mean family size, 51 individuals; range, 21-113; 3535 relative pairs) of African origin on the Caribbean island of Tobago. Written informed consent was obtained from every participant.

Serum glucose was measured using an enzymatic procedure [19]. At the time of analysis, measurements of fasting glucose were complete for 397 individuals. *Diabetes* was defined as fasting serum glucose ≥126 mg/dL or current use of antidiabetic medication. Of the individuals who were classified as having diabetes, 48.4% were currently taking glucose-lowering medication and/or insulin. The coefficient of variation for glucose was 1.8%.

Whole-body DXA measurements were made using a Hologic QDR 4500W densitometer (Hologic, Bedford, MA). Scans were analyzed with QDR software version 8.26a. Regional fat percentages were calculated as follows: (regional fat mass × 100)/(total fat mass). A phantom was scanned daily and reviewed by DXA Resource Group (Worcester, MA) to maintain longitudinal quality assurance of the scanner during the course of the study. The coefficients of variation were assessed by repeated scans with repositioning among 12 individuals and were 0.96% for total fat, 4.5% for trunk fat, 6.0% for leg fat, and 7.5% for arm fat mass.

P values that tested for differences between individuals with and without diabetes were computed using SOLAR (version 2.1.4; Southwest Foundation for Biomedical Research, San Antonio, TX [20]) univariate regression analysis, which accounts for the nonindependence of the family data. Adjusted means were calculated with the "lsmeans" feature of "proc GLM" in SAS (version 9.1; SAS Institute, Cary, NC). Possible significant covariates for each obesity trait were selected based on prior biological and physiological importance reported in the literature. We tested the following covariates: age, sex, height, current smoking, current alcohol intake, physical activity as measured by minutes walking per week, postmenopausal status, parity, age at menarche, and use of oral contraceptives and glucose-lowering medications. We first performed a combined forward and backward stepwise linear regression analysis, ignoring the nonindependence of the subjects, using the R statistical package (version 2.2.1; R Foundation for Statistical Computing, Vienna, Austria) [21]. At this initial screening stage, we used a liberal significance level ($P \leq .10$) to retain the potential significant covariates in the model. We subsequently evaluated each of these potentially significant covariates using a variance components framework that takes into account the correlations among family members. We required $P \leq .05$ for inclusion in our final model for each trait. Because of their relationships with the obesity-related traits, age and sex (+height for the DXA body fat traits) were evaluated as potential covariates in every variance components model even if they were not significant at the initial screening stage. These analyses were performed using SOLAR. Based on the pedigree information, the phenotype information, and the potentially significant covariates, quantitative genetic methods were used to model the total variation in all phenotypic parameters as a function of the mean trait value (additive genetic effects, heritability residual [h2r]), the effects attributed to the measured covariates, and the uncertain variation due to residual genetic and unmeasured environmental factors plus random errors. Bivariate quantitative genetic methods were used in SOLAR to assess the possible genetic and environmental correlations between traits. These methods decompose the total phenotypic correlations (ρ_P) between 2 traits into the portions due to gene or a common set of genes and shared environment effects. To estimate the genetic correlations (ρ_G) and environmental correlations (ρ_E) for pairs of traits, the matrix of kinship coefficients is generated conditioning on all the related individuals within each pedigree. Using standard quantitative genetic theory, the phenotypic variance-covariance matrix and its genetic and environmental components are then obtained. From these matrices, the genetic correlation (ρ_G) can be estimated directly. Likelihood ratio statistics were used to test the significance of ρ_G between any pair of traits. This statistic asymptotically follows a χ^2 distribution, with the degrees of freedom equal to the number of constrained parameters [22].

3. Results

Anthropometric and body fat characteristics of study participants with and without diabetes are shown in Table 1. Compared with individuals with normal glucose levels, individuals with diabetes were older, had a lower proportion of fat stored in their legs ($P = .009$), and to some extent had a higher proportion of fat stored in their arms ($P = .08$), independent of age, sex, and body size. However, the interpretation of analyses of obesity traits by diabetes status

Table 1
Obesity measures by diabetes status

Characteristics	Individuals without type 2 diabetes mellitus (n = 335)		Individuals with type 2 diabetes mellitus (n = 62)		*P* value
	Unadjusted means ± SE	Adjusted means ± SE	Unadjusted means ± SE	Adjusted means ± SE	
Age[a]	39.6 ± 0.9	–	56.9 ± 2.0	–	<.0001
BMI[b] (kg/m^2)	27.8 ± 0.3	28.0 ± 0.3	31.2 ± 0.9	29.9 ± 0.8	.33
Waist circumference[b] (cm)	89.0 ± 0.8	89.6 ± 0.8	95.4 ± 2.8	91.8 ± 2.1	.87
Total fat[c] (%)	27.9 ± 0.6	28.6 ± 0.4	34.1 ± 1.3	30.3 ± 0.9	.51
Trunk fat[c,d] (%)	42.6 ± 0.3	42.8 ± 0.3	45.1 ± 0.8	44.0 ± 0.7	.24
Arm fat[c,d] (%)	13.4 ± 0.2	13.5 ± 0.2	15.7 ± 0.6	14.9 ± 0.6	.08
Leg fat[c,d] (%)	38.6 ± 0.3	38.4 ± 0.3	35.1 ± 0.6	35.9 ± 0.7	.009

[a] *P* value for age was not adjusted.
[b] *P* values for anthropometric traits were adjusted for age and sex.
[c] *P* values for DXA body fat traits were adjusted for age, sex, and height.
[d] Regional fat percentages were calculated as follows: (regional fat mass × 100)/(total fat mass).

may be complicated by the fact that many subjects with diabetes have been treated with glucose-lowering medication at the time of investigation (n = 30). Therefore, to minimize the possible confounding effects of glucose-lowering treatment, we examined the anthropometric and body fat characteristics among diabetic subjects not on glucose-lowering therapy (n = 32, data not shown). However, among this subset of individuals, arm fat (P = .16) and leg fat (P = .10) percentages were no longer related to diabetes. In addition, among all individuals with diabetes, we tested for sex differences in anthropometric traits (adjusted for age) and in DXA body fat traits (adjusted for age and height). Diabetic women (n = 44) had higher BMI (32.7 vs 27.5 kg/m^2, P = .005), higher total percentage fat (39.2% vs 21.0%, P < .0001), and higher proportion of fat stored in their arms (17.6% vs 11.0%, P < .0001) than diabetic men (n = 18). No sex differences among diabetics were observed for waist circumference and for trunk and leg fat percentage (data not shown). However, the number of men with diabetes was considerably smaller than the number of women with diabetes. Therefore, the power to detect sex differences in obesity traits among individuals with diabetes was very limited and should be explored in future larger studies.

Table 2
Phenotypic and genetic correlation between total and central obesity and glucose with fat distribution in the arms and legs

	Arm fat (%)		Leg fat (%)	
	Spearman phenotypic correlation (ρ_P)	Additive genetic correlation (ρ_G)	Spearman phenotypic correlation (ρ_P)	Additive genetic correlation (ρ_G)
BMI[a] (kg/m^2)	0.61*	0.83*	−0.42*	−0.47*
Waist circumference[b] (cm)	0.51*	0.79*	−0.43*	−0.43
Glucose[b] (mg/dL)	0.10[†]	0.18	−0.23*	−0.42[†]

[a] Adjusted for age and sex.
[b] Adjusted for age, sex, and height.
* *P* value < .01.
[†] *P* value < .05.

Residual heritability, the proportion of variance due to additive genetic effects, was estimated after removing the variation attributable to significant covariates. Arm and leg fat was significantly heritable ($h2r_{arm} \pm SE = 0.62 \pm 0.10$ and $h2r_{leg} \pm SE = 0.40 \pm 0.12$, $P < .01$). Significant covariates accounted for 22% and 19% of the total phenotypic variation for arm fat (sex and parity were significant) and leg fat (age, sex, physical activity, and parity were significant), respectively. Sex-stratified analysis showed that the genetic influence on percentage leg fat is much stronger (P = .02) in women ($h2r_{Women} \pm SE = 0.58 \pm 0.18$, $P < .01$) than in men ($h2r_{Men} \pm SE = 0.17 \pm 0.17$, $P > .10$, not significant).

The phenotypic relationships between body fat depots in arms and legs and measures of total and central obesity and glucose are shown in Table 2. Percentage arm fat was positively associated, whereas percentage leg fat was inversely associated, with BMI, waist circumference, and glucose (all P values < .05). We also tested if a common set of genes might influence fat distribution in the arms and legs (Table 2). We observed significant, but not very strong, genetic correlations between percentage leg and arm fat, between percentage leg fat and BMI, and between percentage leg fat and glucose (all P values < .05). In contrast, the genetic correlation between percentage arm fat and BMI and between percentage arm fat and waist circumference was very strong (all P values < .01).

4. Discussion

To our knowledge, this study is the first to investigate the genetic and environmental determinants of DXA measures of body fat distribution in the upper and lower body and their phenotypic and genetic associations with glucose levels and with diabetes in large, multigenerational families of African ancestry. Although obesity is a very important determinant of diabetes risk, the only measure of adiposity significantly and independently associated with diabetes was leg fat. However, after we excluded individuals with diabetes who were currently on glucose-

lowering medications, leg fat percentage was no longer related to diabetes. It is possible that the power to detect significant differences was insufficient because the number of subjects with diabetes decreased from 62 to 32 in this subgroup analysis. Thus, our finding of an inverse association of leg fat with diabetes should be interpreted cautiously and further explored in a larger sample.

African Americans have an increased risk of diabetes even at low BMI levels [13,23], which suggests that the association of BMI with diabetes may be modified by ethnicity. It is also possible that factors other than obesity, such as genetic and environmental factors, might be more prominent risk factors for diabetes among individuals of African ancestry, especially men of African ancestry, who have a relatively low prevalence of obesity [23]. Some studies have shown that leg fat is associated with lower glucose levels, even after adjustment for total and abdominal fat [15-18]. Although arm fat possibly has metabolic characteristics similar to those of leg fat, no association between arm fat and risk of diabetes was found in previous studies [24]. In our study, arm fat was positively associated with diabetes; but this association failed to reach statistical significance. The lack of significant association with this fat depot may be due in part to the small absolute amount of arm fat mass relative to leg fat mass. Alternatively, fat cell activity or different amounts of intermuscular fat in the arms compared with legs might also explain the different associations between leg and arm fat with diabetes.

The mechanisms linking increased adipose tissue accumulation in the lower body and decreased risk of diabetes are still unclear. Some suggest that lower body adipoctyes may have increased insulin sensitivity, thus providing a potential explanation for the inverse association between leg fat and serum glucose concentrations [25]. Subcutaneous fat accounts for up to 90% of the total amount of fat in the legs, and 2% to 6% of leg fat is located intermuscularly [26]. Because leg fat is stored primarily subcutaneously, it is possible that individuals who have a relatively large leg fat mass also store a relatively larger proportion of abdominal fat in the subcutaneous compartment and not in the visceral depot, and thus appear to have lower risk for diabetes. Unfortunately, we were not able to test for associations with diabetes after adjusting for visceral fat because DXA cannot distinguish between abdominal visceral and abdominal subcutaneous fat in the trunk. However, after adjusting for central adiposity, as measured by waist circumference, leg fat was still associated with diabetes in our study ($P < .01$, data not shown).

Importantly, we show for the first time that adipose tissue stored in the extremities is highly heritable and that genes may have a much stronger influence on the distribution of fat in the lower body in women than in men of African origin. To date, there have been no studies on the heritability of arm fat; and only one study reported on the heritability of leg fat ($h2r = 81\%$) [27], although this study was conducted in twins of European origin. We are unaware of studies examining potential sex differences in the genetic influence on upper and lower body fat. Dissimilar strength of genetic influences on leg fat in men and in women may be related to sex differences in susceptibility genes for obesity; sex differences in the ability to deposit fat tissue; interactions with genes on the sex chromosomes; effects related to female reproduction; differences arising from sex-specific hormonal factors; other environmental exposures, such as diet; or even sex differences in adipose gene expression patterns that have been reported [28]. Our findings suggest that subdividing populations by sex may be important for detection of genes for lower body fat distribution and, consequently, genes influencing the risk of diabetes.

Our results additionally imply that only 37% of the covariation between arm and leg fat and 22% of the covariation between BMI and leg fat may be due to shared genes in this Afro-Caribbean population. Therefore, genetic influences on lower body fat may be independent of genetic influences on overall and upper body fat. In addition, approximately 18% of the covariation between leg fat percentage and serum glucose seems to be due to shared genes. In contrast to the weak genetic correlation observed between BMI and waist circumference and leg fat, shared genes are responsible for a considerably larger proportion of the joint variation in BMI and arm fat (69%) and waist circumference and arm fat (62%).

There are several potential limitations of our study. First, we ascertained diabetes without an oral glucose tolerance test; and some misclassification of diabetes was likely to have occurred. Second, our relatively small total sample size and total number of pedigrees may have influenced our heritability estimates. However, previous studies [29,30] have shown that extended pedigrees, such as in the present study, may be more powerful than nuclear pedigrees or sib-pairs in detecting and locating disease loci and with fewer false positives. Therefore, our 8 multigenerational families, which contained thousands of different relationship pairs, should provide a robust estimate of the genetic parameters. Lastly, heritability estimates do not provide insight on the number of loci that contribute to the variation in fat distribution; and therefore, future studies of the genetic mechanisms contributing to these traits are needed.

In conclusion, in this population of African ancestry, leg fat is associated with diabetes independent of overall adiposity. Our findings also provide new evidence for a strong and largely unique genetic contribution to fat storage in the upper and lower extremities, with relatively little covariation between these traits due to shared genes (pleiotropy). In addition, our results suggest that genes may have a stronger influence on the distribution of fat in the lower body in women than in men of African origin. These results suggest that arm and leg fat should be included as obesity-related phenotypes in future genome-wide and candidate gene studies. Such analyses may reveal novel loci and thus new therapeutic targets for insulin resistance and diabetes.

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