Editorial

See corresponding article on page 7.

Causes and consequences of human variation in visceral adiposity[1,2]

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Ectopic fat deposition—that is, adipose tissue accumulation in anatomic regions outside the subcutaneous depot (eg, the visceral cavity, intramuscular compartments, and the pericardial region)—increases cardiometabolic risk factor levels and the risk of diabetes and cardiovascular disease events, whereas elevated abdominal and peripheral subcutaneous adipose tissue may have protective effects. Reduction in ectopic fat accrual may be a profitable cardiometabolic risk prevention target as long as behavioral or physiologic determinants can be identified and safely modified.

A number of deleterious behaviors, including cigarette smoking, physical inactivity, and low dietary fiber intake, while also affecting total adiposity, are more strongly associated with increases in visceral adipose tissue. Prenatal growth restriction, rapid infant weight gain, and chronic hypothalamic-pituitary-adrenal arousal, as observed in depression and psychosocial stress, are further contributors. However, compared with nonmodifiable susceptibility factors (eg, sex and age), which together account for ≈45% of the variation in visceral fat (1), these elements individually contribute substantially less to adipose tissue variation.

Race and ethnicity are additional nonmodifiable factors that contribute to differences in body fat distribution. In this issue of the Journal, Katzmarzyk et al (2) present the largest study to date aimed at quantifying differences in visceral and abdominal subcutaneous adiposity between African American and white adults. The report confirmed that after adjustment for total body adiposity, African American men and women have lower visceral and abdominal subcutaneous adiposity than do whites and provided robust estimates of the magnitude of these differences. Visceral adipose tissue areas (from an axial computed tomography image at the L4–L5 intervertebral space) were ≈15 cm^2 (12%) lower in African American men and ≈20 cm^2 (17%) lower in African American women compared with their white counterparts; subcutaneous adipose tissue differences were smaller. Physical activity, diet, growth and development, hormonal, and other data were not collected to assess whether race differences could be explained in part by these epidemiologic factors. However, because African Americans tend to have more adverse levels of these determinants than do European Americans, it is unlikely that statistical adjustment for these factors would explain the observation; indeed, adjustment for these variables might amplify the race differences.

Circulating concentrations of the antiinflammatory hormone adiponectin are lower and insulin concentrations are higher in African Americans than in whites, which may explain their paradoxically high diabetes risk, despite lower visceral adiposity. Similarly, Asian populations have higher diabetes risk at a lower waist circumference and body mass index (BMI) than do European populations, and lower screening cutoffs for consideration of treatment in Asian populations have been suggested and used (eg, reference 3). Following on the results presented by Katzmarzyk et al (2) and others, are different BMI and waist circumference cutoffs necessary for African Americans? Meta-analysis of abdominal imaging and disease incidence data from existing population-based epidemiologic cohorts of subjects of African ancestry, as was previously conducted for waist circumference (4), is a key next step to discern appropriate screening cutoffs and to evaluate their clinical utility.

Obesity has been hypothesized to have reached epidemic proportions due to the higher inclusive reproductive success of individuals who carry gene variants that predispose to the ability to rapidly store lipids in adipose tissue, which could reasonably buffer these individuals from starvation and loss of fecundity during periods of famine but which exceed needs in periods of plenty (5). The natural selection of varied adipose tissue deposition patterns in humans is more difficult to imagine, because it must invoke a population-variable benefit of allocating excess dietary energy to ectopic fat depots. An interesting hypothesis is that ethnic variation in adipose tissue patterning stems from adaptations to geographic variation in dominant endemic infectious diseases. The functional relation here is in the cross-talk between particular adipose tissue depots and the lymphatic system and specifically the local stimulation of adipocyte lipolysis to support lymphocyte proliferation near the site of infection, which varies by disease and by geographic region (6). Preferential ectopic adipose tissue growth and systemic inflammation may thus be the deleterious vestige of immunologic defense strategies shaped to particular disease landscapes.

Regardless of how the genetic control of visceral adiposity may have been shaped over evolutionary history, there is certainly evidence that such genes will be found, and that they may vary

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across populations. First, adipose tissue patterning is significantly heritable; additive genetic effects explain ≈40–60% of the variance in visceral and subcutaneous adipose tissue mass (7). Second, European genetic admixture in African American subjects is positively associated with BMI-adjusted waist circumference (8). Third, recent genome-wide association studies (thus far restricted to studies of anthropometric proxies such as waist circumference) in European or European American cohorts have identified a small set of genes that are preferentially associated with central adiposity (9, 10). These include *TFAP2B*, *MSRA*, and *LYPLAL1*, which are expressed in adipocytes and regulate glucose transport, and lipolysis, and *NRXN3*, which is expressed in the central nervous system. Studies are currently underway to determine whether allelic variations at these and/or other genetic loci have similar association with central adiposity in African Americans and whether or not they occur at similar frequencies. Significant work remains to identify the functional variant or variants at each locus (which may be easier in populations that exhibit lower average linkage disequilibrium, as in individuals with African ancestry) and to characterize how they may interact with sex, age, and behavioral factors. It is expected that common variants that predispose to elevated visceral adiposity will explain only a small proportion of the phenotypic variance, as observed for other common disease traits. Epigenetic modification of identified genes via dietary or other exposures that differ by race may result in differential gene expression levels that will explain additional variation in adipose tissue patterning.

Understanding why African American adults have lower visceral adiposity, on average, despite carrying a higher burden of risk factors that generally increase adiposity, is a fruitful avenue for transdisciplinary genetic and environmental research. Elucidation of the molecular origins of sex and age variation in ectopic fat deposition, which are equally unclear and of even greater magnitude, may reveal additional targets for diabetes and cardiovascular disease prevention.

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