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EDITORIAL COMMENT

Time to Retire the BMI?

Evaluating Abdominal Adipose Tissue Imaging as Novel Cardiovascular Risk Biomarker*

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Body mass index (BMI) is the currently recommended adiposity-related biomarker for identifying individuals at elevated risk of cardiovascular disease (CVD), type 2 diabetes, and all-cause mortality (American College of Cardiology/American Heart Association Class I, Level of Evidence: B) (1). If one were to evaluate critically the performance of BMI as a biomarker, however, it would fall short in several areas. First, although higher BMI grossly identifies individuals in the population at increased risk for mortality, those who are overweight or mildly obese may have lower or similar mortality compared with normal-weight individuals (2). Second, approximately one-third of obese adults are metabolically healthy (defined as 0 or 1 cardiometabolic risk factor) and remain free of cardiometabolic disease (3). Third, BMI has never emerged as a component of the Framingham (4) or Pooled Cohort Equation (5) CVD risk scores, because it does not add sufficient discriminatory capacity over traditional risk factors. Finally, higher-BMI individuals may even demonstrate an "obesity paradox" with lower rates of mortality and morbidity from established CVDs compared with those with normal BMI (6). These important limitations create an opportunity for new adiposity-related biomarkers to emerge that will impact clinical cardiovascular care while improving on the inherent shortcomings of BMI assessment.

Enter abdominal adipose tissue imaging. Both visceral (intra-abdominal) adipose tissue (VAT) and abdominal subcutaneous adipose tissue (SAT) can be directly imaged with computed tomography (CT) or magnetic resonance imaging (MRI). Dual x-ray absorptiometry is also being increasingly used to estimate VAT and SAT with the added benefits that it circumvents many of the limitations of CT and MRI including prolonged scan time (with MRI), high cost, and radiation (with CT) (7). VAT, and questionably SAT, distribution contribute to the heterogeneity of risk seen among high-BMI individuals (8). Excess VAT in obese adults is associated with insulin resistance, atherogenic dyslipidemia, and hepatic steatosis (9). We have shown that higher VAT mass is associated with increased risk of developing type 2 diabetes (10) and CVD (11) and that this effect is independent of BMI. Important for evaluation of any novel biomarker is whether it is modifiable by purposeful interventions to select the appropriate intervention or monitor response to therapy. As shown in multiple studies, both observational and interventional (including randomized controlled trials) (12,13), VAT and SAT meet this criterion and may represent key biomarkers prepared to supplant the role of BMI alone in CVD risk stratification paradigms.

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In this issue of the *Journal*, Lee et al. (14) report on the association of changes in abdominal adipose tissue volume (quantity) and attenuation (so-called "quality") on CT with CVD risk markers among 1,106 participants enrolled in the Framingham Heart

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Study Third Generation cohort. During a mean follow-up period of 6.1 years, the authors found that participants gained an average of 0.55 kg of abdominal SAT and 0.65 kg of VAT. These changes represent a 22% increase in SAT and a 45% increase in VAT from baseline. It is important to note that the vast majority of abdominal adipose tissue is stored in SAT with the VAT depot usually representing one-third or less of total abdominal fat. The strikingly discordant relative increase in VAT compared with SAT in the present study should clue us in to a major premise—that the inability to expand the SAT depot in the face of caloric surplus, resulting in the greater relative expansion of VAT, may be the underlying physiological derangement predisposing to worsening CVD risk factors. The authors report the following 2 primary findings: 1) longitudinal increases in VAT and SAT volume were associated with incident and worsening CVD risk factors; and 2) associations persisted after adjustment for BMI, waist circumference, and baseline adipose tissue volume. Although changes in both adipose depot quantities were associated with incident and worsening CVD risk factors to some degree, the associations with VAT were more robust. Unfortunately, VAT and SAT changes were not modeled jointly in this analysis, which should have been possible because the correlation in these 2 depots is only modest. Thus, we are unable to tease out whether the associations seen with SAT are truly independent of VAT or whether they would be significantly attenuated when the confounding impact of VAT is taken into account. For example, in a recent analysis of normotensive participants in the Dallas Heart Study, when VAT, SAT, and lower body fat were entered into a multivariable model together, only VAT remained independently associated with incident hypertension (15). It will be crucial for future outcomes studies to assess the relationships of specific fat compartments jointly to better evaluate the individual depot contributions to risk.

The authors also report that longitudinal decreases in fat attenuation in Hounsfield units (HU) on CT (as a surrogate for worsening fat "quality") were associated with incident and worsening CVD risk factors, independent of baseline fat volume. This work is an extension of a previous report demonstrating that low CT attenuation in SAT and VAT were associated with CVD risk markers in the same cohort in cross-sectional analysis (16). Although the theoretical concept that lower HU signifies greater lipid accumulation and overactive lipolysis is intriguing, the significance of fat attenuation is far from clear. Other studies performed in the Framingham cohort have shown opposite findings that lower fat density is associated with less subclinical atherosclerosis (17), lower all-cause mortality (18), and lower CVD risk factor burden (19). It is also plausible that greater attenuation (higher HU) may represent fibrosis due to localized hypoxia or hypercellularity from macrophage infiltration related to dysfunctional adipose tissue (20). The determinants of adipose attenuation change on CT are also not well understood; whether CT fat attenuation is sensitive to dietary fluctuations, physical activity, or medication effects are unknown. Additional studies are needed correlating decreased CT attenuation with in vivo assays of adipose tissue function before this biomarker can be accepted as an indicator of adipose function or quality.

Several technical issues merit comment. Because the mean attenuation of VAT actually increased over the course of the study (+0.07 HU for VAT compared with -5.5 HU for SAT) and the SD of VAT attenuation change was quite narrow (<0.2 HU), the authors' decision to model a 5 HU decrease in VAT (>25 times the SD change) may be misleading. Also, we suggest caution regarding interpretation of the magnitude and even the direction of changes in the adipose imaging parameters. Interscan reproducibility has not been proven for CT-based fat attenuation and, given the narrow range of attenuation at baseline with relatively small changes over time, it may be difficult to discern if changes represent true structural alterations in adipose tissue or solely reflect inherent variability in the measurement. Finally, calibration is a thorny issue when imaging studies are applied in longitudinal cohort studies, and although miscalibration would not be expected to influence the relationship between exposure and outcome variables, it may lead to erroneous conclusions regarding the size and direction of changes over time.

The findings in the study by Lee et al. (14) support a growing body of data that clearly demonstrate that adipose tissue imaging, which allows anatomical characterization of regional fat depots, provides important information about cardiometabolic risk not contained in the simple BMI measurement. There remain a number of important questions for additional study. How can we assess fat function or dysfunction while circumventing the invasive nature of tissue biopsy or cell culture assay? What biological correlate would accurately represent adipose tissue function and be stable over time with minimal measurement variation or sensitivity to temporal change, yet be modifiable by interventions that are known to improve adipose function? Thus, the

ultimate question is whether it is possible to translate evaluation of "form" (the anatomical measurement of adipose depots) to assessment of "function," to unravel the pathophysiology of adipose tissue expansion, and circumvent the inherent limitations of BMI and isolated imaging-based fat quantification.

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