Visceral Adipose Tissue: At the Intersection of Lipoprotein Associated CV Risk

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Obesity is a global epidemic that increases the risk of type 2 diabetes, cardiovascular disease, and other medical conditions that lead to premature mortality and more years lived with disability [1]. However, obesity is a heterogeneous disorder in which the fat distribution confers differential cardiometabolic risks [2]. In most studies, anthropometric measures of abdominal fat are superior measures of incident coronary heart disease events than is total adiposity estimated by the body mass index (BMI) is [3–10]. Associations between coronary heart disease risk factors and events are stronger when visceral adipose tissue (VAT) is measured directly by computerized tomography or magnetic resonance imaging than by indirect measures of central adiposity such as the waist circumference or the waist-hip ratio or estimated by BMI [11–15]. High VAT area has also been more strongly associated with characteristics of vulnerable plaque than low VAT area or other body compositional measures that included subcutaneous adipose tissue area, waist circumference, and BMI [16]. Specifically, VAT was associated with noncalcified plaque burden as assessed by computerized tomography angiography, as well as the presence of noncalcified plaque with positive remodeling and spotty calcium that represent other characteristics of vulnerable plaque.

VAT is more metabolically active than subcutaneous adipose tissue is, which results in increased flux of nonesterified fatty acids into the portal circulation. The nonesterified fatty acids serve as substrates for triglyceride production, which is incorporated into large very low-density lipoprotein (VLDL) particles. Overproduction of large VLDL particles and impaired catabolism in insulin-resistant individuals results in transfer of core triglyceride into LDL and high-density lipoprotein (HDL) particles. Triglyceride-enriched LDL and HDL particles are substrates for lipases that hydrolyze the triglyceride resulting in smaller LDL and smaller HDL particles. Small LDL particles are considered more atherogenic than large LDL particles because of reduced clearance by LDL receptors and increased oxidative susceptibility per particle.

High concentrations of large VLDL particles and small LDL particles and low concentrations of large HDL particles are associated with higher rates of coronary artery disease in men [17] and predict future risk of incident type 2 diabetes in previously healthy women [18]. High LDL particle concentrations, particularly small LDL particles, predict incident and recurrent cardiovascular events in population-based cohorts [19,20] and among coronary heart disease patients treated with lipid-lowering therapy [21]. Low HDL particle concentrations are associated with increased cardiovascular events in population-based studies [22,23] and clinical trials of lipid-modifying therapies in multivariate models [21,24]. The reported associations from these prospective studies and clinical trials that examine cardiometabolic risk and lipoprotein subclasses were significant in multivariate models that included indirect measures of adiposity such as BMI; however, none of the reports measured adiposity directly.

In this issue of *Global Heart*, Hirooka et al. [25] investigated the association between multiple measures of adiposity (computerized tomography and anthropometric) and nuclear magnetic resonance–measured lipoprotein subclasses from a population-based sample of middle-aged men of Japanese, Korean, and African American ancestry. VAT was more strongly associated with high concentrations of total LDL and VLDL particles and small LDL particles and lower concentrations of large HDL particles than subcutaneous adipose tissue, waist circumference, and BMI in multivariate analysis that adjusted for age, smoking, and alcohol consumption. The association of VAT with these lipoprotein subclasses was similar regardless of ancestry. Unfortunately, the investigators did not report whether these lipoprotein subclass associations were different than those for plasma triglycerides and HDL cholesterol, which are measures that have been correlated with VAT in other studies [11,12] and incorporated into the visceral adiposity index [2].

It is important to ask what clinically relevant information has been learned from the current study and what information is required from future studies. VAT is more strongly associated with cardiometabolic risk factors in several studies including this report from Hirooka et al. [25], and thus future reports that investigate the cardiometabolic risk of adiposity will require VAT measurements. Yet, it remains uncertain whether VAT and certain lipoprotein abnormalities (high VLDL particle concentration, high LDL particle concentration, or low levels of large HDL particle concentration) considered in isolation or in aggregate provide incremental information concerning the risk of type 2 diabetes, atherosclerosis, or cardiovascular events. Prospective studies will be required to address the interactions of VAT and lipoprotein subclasses and their functional properties on incident type 2 diabetes and cardiovascular disease in ethnically and racially diverse populations of men and women [26].

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