Editorial Commentary

Indices of Obesity and Cardiometabolic Risk

Adam Whaley-Connell, James R. Sowers

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The prevalence of obesity in the United States has increased dramatically during the past 25 years.[1] Many of the population-based cohort studies in the past decade have defined cardiovascular disease (CVD) risk associated with obesity in the context of diabetes mellitus and hypertension based on measurement of body mass index (BMI).[2–4] It is not as clear which clinical measures of obesity to use in risk prediction for diabetes mellitus, hypertension, and CVD morbidity and mortality.[2–5] In this issue, Bombelli et al[6] explore the predictive value of BMI and waist circumference (WC) on risk prediction for new-onset impaired fasting glucose and diabetes mellitus, hypertension, and left ventricular hypertrophy (LVH). A prospective cohort of ≈3200 individuals from Italy were followed over 10 years with anthropometric measures of weight (BMI and WC), insulin sensitivity (fasting glucose and insulin), blood pressure (in- and out-of-office and ambulatory), and LVH by echocardiography. The population was risk stratified based on BMI and WC to determine new-onset insulin resistance, diabetes mellitus, hypertension, and LVH based on quintiles of relative risk. There was a graded relationship between increasing BMI, in the range of 21 to 29 kg/m^2, and increasing risk for new-onset impaired fasting glucose, diabetes mellitus, and hypertension that became significant in the higher (eg, fourth and fifth) quartiles of BMI (>26 kg/m^2). Unique to this investigation is the addition of WC for risk prediction, and, concordant with the BMI data, there was a similar graded relationship between increasing WC and risk. Although new-onset ambulatory hypertension and LVH were better predicted by baseline WC than BMI, the overall strength of risk prediction did not increase when adding WC to BMI in adjusted analysis and was comparatively similar on the adjusted risk of developing conditions (receiver-operating characteristic) analysis. These data confirm reports that WC may add limited predictive ability to that of BMI[7,8] in cardiometabolic risk prediction.

The use of WC in risk prediction has been suggested by recent preclinical and limited clinical data, which support the notion that the association between diabetes mellitus and hypertension with central obesity (eg, WC) is stronger than the association with BMI. Numerous studies using imaging modalities or anthropometric measures (including waist:hip ratio) have provided additional credence that visceral adipose tissue is the major contributor to cardiometabolic complications, such as diabetes mellitus and hypertension.[7,8] In this context, obesity is a state of metabolic dysregulation driven by inappropriate activation of the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system despite a state of relative volume expansion.[9] RAAS activation in obesity promotes alterations in biochemical mechanisms that include insulin-dependent metabolic signaling. In traditional insulin-sensitive tissues (eg, skeletal muscle, fat, and liver), and in cardiovascular tissue, alterations in insulin metabolic signaling promote impairments in glucose disposal and cardiovascular metabolic signaling that contribute to the development of hypertension and diabetes mellitus (Figure).[9] However, increased WC does not always reflect visceral obesity, because it may be related to increased abdominal subcutaneous fat. Although the Figure implies that visceral obesity causes hypertension and diabetes mellitus via insulin resistance, mediated effects on endothelial dysfunction, RAAS activation, and impaired glucose uptake, there are likely other important mechanisms involved.

When insulin binds to the insulin resistance, phosphorylation of intracellular substrates, including insulin resistance substrate family members, serves to engage downstream phosphoinositide 3-kinase. Phosphoinositide 3-kinase then binds to the pleckstrin-homology domain in 3-phosphoinositide dependent protein kinase 1, resulting in its phosphorylation and activation of other serine-threonine kinases, including protein kinase B (Akt) and atypical protein kinase C isoforms, which mediate a number of metabolic actions, including GLUT-4 translocation to membranes, endothelial NO synthase activation, and cardiac and vascular relaxation.[9,10] In obesity, RAAS and sympathetic nervous system activation promote a pro-oxidative/proinflammatory milieu that contributes to impairments in insulin metabolic signaling resulting in reduced glucose disposal, as well as alterations in cardiovascular function.

Much of the clinical work to date, establishing the link between obesity and hypertension, has used in-office readings. Recent work in clinical hypertension has attempted to validate out-of-office and ambulatory monitoring in risk-prediction models.[3–6] The longitudinal data from the current study indicate that out-of-office and ambulatory monitoring are equally important to in-office measures in risk stratification of the obese population. Similar to in-office measures, receiver-operating characteristic analysis showed a similar graded relationship over 10 years between BMI and WC and

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From the University of Missouri Cardiovascular and Diabetes Center (A.W.-C., J.R.S.), Department of Internal Medicine (A.W.-C., J.R.S.), Department of Medical Pharmacology and Physiology (J.R.S.), and Harry S. Truman Veterans Affairs Medical Center (A.W.-C., J.R.S.), University of Missouri, Columbia, MO.

Correspondence to James R. Sowers, University of Missouri, D109 Diabetes Center HSC, One Hospital Dr, Columbia, MO 65212. E-mail sowersj@health.missouri.edu

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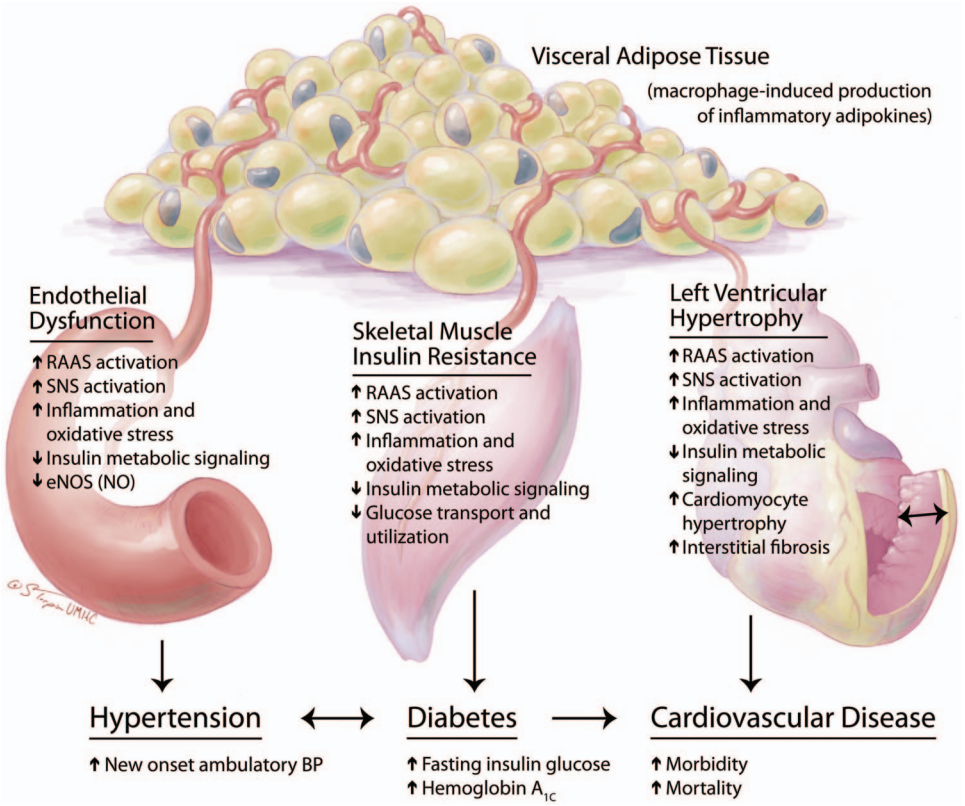

Figure. The relationship between increased visceral adipose tissue with an increased risk for endothelial dysfunction that manifests as hypertension, insulin resistance, and overt diabetes mellitus with left ventricular hypertrophy and long-term cardiovascular risk. RAAS indicates renin-angiotensin-aldosterone system; SNS, sympathetic nervous system; BP, blood pressure.

development of new-onset hypertension as determined by out-of-office and ambulatory monitoring measurements.

One important long-term risk associated with obesity, hypertension, and impaired insulin metabolic signaling is the development of LVH.[10] In preclinical and clinical models, LVH has been validated as a prognosticator for future CVD events. Impaired insulin metabolic signaling, in conjunction with RAAS and sympathetic nervous system activation, is an important factor in the genesis of maladaptive myocardial remodeling.[10] In the myocardium, insulin normally promotes glucose uptake and use, mitochondrial ATP production, and endothelial NO synthase activation and inhibits ischemia-induced apoptosis. In conditions of obesity and inappropriate RAAS activation, there is both myocardial hypertrophy and increased fibrosis, leading to LVH and myocardial systolic and diastolic dysfunction.[10] Thus, impaired insulin metabolic signaling in cardiovascular tissue may explain the link among obesity, hypertension, LVH, and increased CVD risk (Figure).

In summary, BMI is conventionally used as a measure of obesity, yet there has been concern that this measure may not capture the relationship among visceral adiposity, insulin resistance, vascular endothelial dysfunction, and maladaptive cardiac remodeling. The current study[6] indicates that baseline BMI and WC had comparable predictive value for new-onset diabetes mellitus and in-office hypertension, whereas new-onset ambulatory hypertension and LVH are better predicted by baseline WC than BMI. Collectively, these longitudinal data from the Pressioni Arteriose Monitorate e Loro Associazioni Study population suggest that the combined use of WC and BMI as obesity indices has potentially greater use than just BMI as a predictor of cardiometabolic risk. Because all of the patients in the Pressioni Arteriose Monitorate e Loro Associazioni Study cohort were white, studies in more racially diverse populations will be necessary to demonstrate the generalizability of the utility of using both BMI and WC as predictive indicators of CVD risk.

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