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EDITORIAL COMMENT

Coronary Microvascular Dysfunction

A Preferred Risk Marker in Obesity?*

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The prevalence of obesity has been continuously increasing in industrialized nations, exceeding one-third of the adult population in North America, of whom >3% have even morbid obesity (body mass index [BMI] ≥40 kg/m^2) (1). As obesity has been appreciated as a pivotal risk factor of cardiovascular morbidity and mortality, the obesity epidemic raises substantial public health concern (1). An impairment of the vasodilatory capacity of the coronary circulation has been widely recognized to precede structural alterations of the coronary artery disease (CAD) process or heart failure manifestation in cardiovascular risk individuals, which carries important diagnostic and prognostic information (2). Previous positron emission tomography (PET) flow studies (3-5) have demonstrated an association between obesity and an impairment of coronary circulatory or microvascular function. These studies were performed in so-called metabolically healthy obese individuals defined as obesity without metabolic abnormalities such as arterial hypertension, dyslipidemia, and hyperglycemia. A disturbance of coronary microvascular function can be seen as an important "integrating index" of the total stress burden imposed by a variety of cardiovascular risk factors on the arterial wall as well as other yet unknown determinants and genetic predispositions (2,6). In this respect, the interrelation among obesity clustered to other traditional cardiovascular risk factors, coronary microvascular (dys)function, and prognosis has not been truly investigated.

In this issue of the *Journal*, Bajaj et al. (7) report that a disturbance of coronary microvascular dysfunction was independently associated with elevated BMI and adverse outcome in individuals with traditional cardiovascular risk factors.

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In particular, coronary microvascular dysfunction appeared to be superior to BMI in cardiovascular risk prediction, which may have implications in risk management and treatment planning of obese individuals beyond BMI and traditional cardiovascular risk factors, as the authors state (7). The study evaluation was conducted in a retrospective fashion in a cohort of 827 cardiovascular risk individuals undergoing rest and stress myocardial perfusion imaging with ^{13}N-ammonia or ^{82}rubidium PET for evaluation of suspected CAD based on clinical symptoms. All patients had PET-determined normal myocardial rest-stress perfusion, while global myocardial flow reserve (MFR) was quantified noninvasively for the identification and characterization of coronary microvascular dysfunction. Clinical endpoints were determined over a relatively long median follow-up period of 5.6 years. The occurrence of a first major adverse event, defined as a composite of death or hospitalization for nonfatal myocardial infarction or heart failure was evaluated during the follow-up. The observations were 4-fold: 1) there was a J-shaped association between MFR and BMI so that higher BMI in obese patients was independently associated with worsening coronary microvascular function; 2) both MFR and BMI proved to be predictive for major adverse events, while only MFR remained as an independent predictor for outcome and appeared to be a better discriminator of cardiac risk than were BMI and traditional cardiovascular risk factors; 3) obese individuals with an MFR ≤1.7 had a ≥2.5-fold increased risk of cardiac events that was most evident in patients without extreme obesity (BMI ≥30

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but <39 kg/m^2); and 4) the increased risk of events was not affected by the indications for bariatric surgery in morbid obese patients. The observed J-shaped association between MFR and BMI is widely in agreement with previous clinical investigations in obese individuals (3-5,8), but expands these findings now to a large cohort of obese individuals having concomitant classical cardiovascular risk factors such as arterial hypertension, dyslipidemia, diabetes mellitus, and smoking. In the adjusted analyses, MFR remained as an independent predictor of major adverse events. Interestingly, despite a progressive worsening of coronary microvascular function with increasing BMI in obesity and morbid obesity, the major adverse event rate was highest in patients with a BMI ranging from 30 to 39 kg/m^2, but less in morbid obese individuals. This might be explained in part by different metabolic disease entities that obesity and morbid obesity may reflect (4). For example, there is a distinct and nonlinear elevation in insulin resistance, plasma levels of insulin, and systemic inflammation from obesity to morbid obesity, while no further alterations in decreases in high-density lipoprotein cholesterol and increases in triglyceride are commonly noted. This discordant observation likely is related to differences in adipose tissue distribution. In nonmorbid obesity, increases in visceral adipose tissue lead to higher fatty acid provision from the abdominal area that adds to greater detrimental metabolic abnormalities than subcutaneous fat accumulation. Conversely, increases in subcutaneous adipose tissue, as commonly observed in morbid obesity, may rather confer a relative protection against the risk of CAD development, owing to a lower lipolytic response to catecholamines, a higher antilipolytic sensitivity to insulin, and an enhanced lipoprotein lipase activity (4). Such metabolic alterations were also paralleled by microvascular dysfunction in that endothelial- and endothelium-independent coronary flow responses did not further worsen from obesity to morbid obesity (4,5,8). In morbid obesity, metabolically triggered systemic inflammation and increases in leptin plasma levels have been demonstrated to be associated with somehow maintained coronary endothelial function (4). Thus, yet unknown factors related to systemic inflammation and increased releases of adipocytokines such as leptin or adiponectin may indeed confer some vascular protection against the classical adverse effects of body fat such as low high-density lipoprotein cholesterol, dyslipidemia, and insulin-resistance syndrome. Therefore, current and previous observations (3-5,8) may give rise to a new concept that a "dysbalance" among obesity-related metabolic changes, endocannabinoids, and adipocytokines may account as a pivotal determinant of microvascular dysfunction in obesity. Albeit that obesity has been put forth as a major risk factor for CAD and related heart failure manifestation, it has also been appreciated as an independent predictor of systolic and, in particular, diastolic heart failure, owing to its adverse effects on cardiac structure, implying the initiation of interstitial fibrosis, and concentric or eccentric left ventricular hypertrophy (1). As study patients had normal left ventricular function at baseline assessment, the clinical heart failure manifestations during follow-up are likely related predominantly to clinically manifest left ventricular diastolic dysfunction and less likely to a global decrease in systolic function. Such structural alterations may also manifest clinically as sudden cardiac death due to disturbance of left ventricular repolarization with potential induction of ventricular arrhythmias. Unfortunately, more detailed information on the single events of the composite endpoint is missing, which would have been of further interest to gain insight on the prevalence of ischemic and nonischemic causes of cardiac events in the current obese study population.

Taken together, the observations of the current study reported by Bajaj et al. (7) are unique because they provide important evidence that obesity in cardiovascular risk individuals is not just an epiphenomenon, but rather it actively contributes to the manifestation of coronary microvascular dysfunction associated with adverse cardiac outcome. It is critical to note that a relatively normal MFR exceeding 1.7 resulted indeed in less cardiac events than in those obese individuals with an MFR of <1.7 (15% vs. 29%; $p = 0.002$). Thus, there was still a substantial portion of 15% of cardiac events in the obesity group despite subnormal MFR, likely related predominantly to direct adverse effects of obesity or traditional cardiovascular risk factors on cardiac structure needing further clinical evaluation. In this respect, it appears advisable that, apart from primary preventive medical care to control for cardiovascular risk factors, treatment strategies should always imply weight reduction and continuous physical exercise in obese individuals, independent of the presence or absence of coronary microvascular dysfunction (9,10).

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