Targeting abdominal obesity in cardiology: Can we be effective?

Paul Poirier MD PhD FRCPC FACC FAHA

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Obesity has reached epidemic proportions in much of the industrialized world, and is also increasing in prevalence in the developing world. In the later decades of the 20th century until present, there have been numerous epidemiological studies reporting the relationship between excess weight and total, or all-cause, mortality. Obesity is associated with a wide variety of comorbidities such as type 2 diabetes, systemic hypertension, cardiovascular disease, certain cancers and sleep apnea, most of which may lead to disability or death. In general, the risk of developing comorbidities such as diabetes and cardiovascular disease rises as body mass index (BMI) increases. Using BMI, an indicator of relative weight for height (kg/m^2) and a frequently used surrogate for assessing excess body fat, epidemiological studies have found linear, U- or J-shaped relationships between total mortality and BMI. However, obesity is remarkably heterogeneous. Obese patients considered to be 'at risk' are mostly characterized by features associated with the metabolic syndrome. The aim of the present paper is to review the cardiovascular consequences of obesity and to review some of the literature emphasizing why the cardiologist should measure other indices of adiposity in order to refine clinical assessment of obese individuals.

Key Words: *Adiposity; Comorbidities; Metabolic syndrome; Obesity*

Obesity has reached epidemic proportions in the United States as well as much of the industrialized world, and is increasing in prevalence in the developing world (1). In the most widely used classification of body mass, body weight is expressed in terms of body mass index (BMI) (1). Obesity is defined as a BMI of 30 kg/m^2 or greater, which is further subdivided into grades (Table 1). A new category, defined as 'super obese', has been reported in the literature. Indeed, the most rapidly growing segment of the obese population are the severely obese and super obese (2). Between 1986 and 2000, the number of individuals with a BMI greater than 30 kg/m^2 , 40 kg/m^2 and 50 kg/m^2 is reported to have doubled, quadrupled and quintupled, respectively, in the United States (3). In general, the risk of developing comorbidities such as diabetes and cardiovascular disease (CVD) rises as BMI increases. Using BMI, an indicator of relative weight for height (kg/m^2) and a frequently used surrogate for assessing excess body fat, epidemiological studies have found linear, U- or J-shaped relationships between total mortality and BMI. However, obesity is a remarkably heterogeneous condition in which the distribution of the adipose tissue is of importance in determining the presence or absence of metabolic dysfunctions (4). Although obesity as defined by the BMI is undoubtedly associated with an increased rate of comorbidities and cardiovascular mortality (5,6), obese individuals considered to be 'at risk' are mostly characterized by features associated with the metabolic syndrome (MetS) (4,5).

Cibler l'obésité abdominale en cardiologie : Pouvons-nous être efficaces ?

L'obésité a atteint des proportions épidémiques dans la plupart des pays industrialisés, et sa prévalence augmente dans les pays en voie de développement. Depuis les dernières décennies du XX^e siècle jusqu'à maintenant, de nombreuses études épidémiologiques ont porté sur le lien entre l'excès de poids et la mortalité totale ou toutes causes confondues. L'obésité s'associe à toute une série de comorbidités, telles que le diabète de type 2, l'hypertension systémique, les maladies cardiovasculaires, certains cancers et l'apnée du sommeil, dont la plupart peuvent provoquer une incapacité ou un décès. En général, le risque de développer des comorbidités telles que le diabète et les maladies cardiovasculaires est proportionnel à l'indice de masse corporelle (IMC). À l'aide de l'IMC, un indicateur de poids par rapport à la taille (kg/m^2) et un substitut fréquent pour évaluer l'excès d'adiposité, les études épidémiologiques ont permis de découvrir des relations linéaires, en U ou en J entre la mortalité totale et l'IMC. Toutefois, l'obésité est d'une remarquable hétérogénéité. Les patients obèses considérés comme vulnérables se caractérisent surtout par des manifestations reliées au syndrome métabolique. Le présent article vise à analyser les conséquences cardiovasculaires de l'obésité et certaines publications soulignant que le cardiologue devrait mesurer d'autres indices d'adiposité pour perfectionner son évaluation clinique des personnes obèses.

DEFINITION OF OBESITY

The improvement in risk factor recognition and management that developed through the years in cardiology may be challenged by today's youth, who will carry their elevated risk of CVD for many more years (7). The estimated years of life lost due to obesity differs among races and between the sexes (8). It appears that obesity as defined solely by the BMI cannot always discriminate between the individuals at higher risk of developing CVD. Actually, nonobese overweight patients with an excess of visceral adiposity, thus at higher risk, would not be detected on the basis of BMI alone (9). Waist circumference (WC) or waist-to-hip ratio (WHR) has been used as a proxy measure for body fat distribution when assessing the health risk increased with increasing ratio. WC reflects abdominal or intra-abdominal fat, and hip circumference reflects different aspects of body composition in the gluteofemoral region (ie, muscle mass, bone and fat mass). As mentioned earlier, possible explanations for a lack of consistency and reproducibility of the relation between BMI and death may be due to the covariance of BMI with other cardiac risk factors, unmeasured confounders, or misclassification bias from the use of surrogate markers of obesity. Abdominal obesity has been reported as a risk factor for CVD worldwide and is likely a better clinical surrogate marker of obesity risk than BMI (9-12). This has been reported in men (13), women (14) and in large cohorts (10,11,15-20). In addition, the

Institut universitaire de cardiologie et de pneumologie, Laval Hospital, Sainte-Foy, Québec

Correspondence: Dr Paul Poirier, Associate Professor/Laval University Faculty of Pharmacy, Institut universitaire de cardiologie et de pneumologie/Laval

Hospital, 2725 Chemin Sainte-Foy, Sainte-Foy, Québec G1V 4G5. Telephone: 418-656-4767, fax 418-656-4562, e-mail Paul.Poirier@crhl.ulaval.ca

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TABLE 1
Classification of body weight according to body mass index

Classification	Body mass index
Underweight	<18.5 kg/m ²
Normal or acceptable weight	18.5 kg/m ² to 24.9 kg/m ²
Overweight	25 kg/m ² to 29.9 kg/m ²
Obese	≥30 kg/m ²
Grade 1	30 kg/m ² to 34.9 kg/m ²
Grade 2	35.0 kg/m ² to 39.9 kg/m ²
Grade 3	≥40 kg/m ² (severe, extreme or morbid obesity)
'Super' obese	≥50 kg/m ²

odds of prevalent atherosclerosis, defined by coronary artery calcium score, have been reported to be greater for each quintile of WHR and WC compared with each quintile of BMI in both women and men (21). Although some uncertainty about the MetS exists (22), it remains useful in identifying CVD risk that portends beyond low-density lipoprotein cholesterol. At present, two definitions are commonly employed to define the MetS (Table 2).

CARDIAC CONSEQUENCES OF OBESITY

Heart function

There are numerous cardiac consequences of obesity (Table 3). Changes in cardiac hemodynamics associated with obesity may alter left ventricular structure and function and ultimately cause congestive heart failure (CHF). Excess obesity is associated with an increased risk of developing CHF (1) but once the patient presents with CHF, the presence of obesity may not adversely affect the patient's outcome (1). This has been described as the 'obesity paradox'. This may be related to the definition of obesity because, using abdominal obesity as a measurement of adiposity, it was shown that abdominal body fat distribution may be a stronger risk factor for CHF than overall obesity (23). No outcomes studies have been reported as yet.

Electrocardiography

The electrocardiogram is influenced by the morphological changes induced by obesity such as displacement of the heart by elevating the diaphragm in the supine position, increasing the cardiac workload with associated cardiac hypertrophy, increasing the distance between the heart and the recording electrodes induced by the accumulation of adipose tissue in the subcutaneous tissue of the chest wall (and possibly increased epicardial fat), and the associated chronic lung disease secondary to the sleep apnea/hypoventilation syndrome. In a large cohort of obese individuals, the heart rate, PR interval, QRS interval, QRS voltage and corrected QT (QTc) interval all showed an increase with increasing obesity (24). Of clinical importance, approximately 8% of patients presented with a QTc greater than 0.44 s and approximately 2% presented with a QTc greater than 0.46 s. Interestingly, prolongation of the QTc interval has been shown to be associated with visceral obesity in healthy premenopausal women (assessed by computed tomography), independently of obesity and other risk factors (25). Serious cardiac arrhythmias and conduction abnormalities related to obesity per se are rare (1). Most commonly, arrhythmias may be secondary to hypoxia due to sleep apnea but also include atrial fibrillation (AF), atrial flutter, ventricular tachycardia and bradyarrhythmias related to sinus node dysfunction. Obesity has been shown to be an independent risk factor for AF with an adjusted 50% risk increase for developing AF (1) and higher radiation dose during AF ablation procedures (26).

TABLE 2
Definitions of the metabolic syndrome

	ATPIII 2001/2005 (≥3 of the following)	International Diabetes Federation 2005
Central obesity (WC)	>102 cm (M), >88 cm (F)	≥94 cm (M) ≥80 cm (F) <i>Plus ≥2 of the following:</i>
Dyslipidemia		
Triglycerides	≥1.7 mmol/L or medication	≥1.7 mmol/L
HDL cholesterol	<1.0 mmol/L (M), <1.1 mmol/L (F)	<0.9 mmol/L (M) <1.1 mmol/L (F)
Hypertension	≥135/85 mmHg or medication	≥130/85 mmHg or medication
Fasting plasma glucose	≥6.1 mmol/L (2001) ≥5.6 mmol/L (2005)	≥5.6 mmol/L

ATP Adult Treatment Panel; BMI body mass index; F Female; HDL High-density lipoprotein; M Male; WC Waist circumference. Data from reference 5

Coronary artery disease

The atherosclerotic process begins at a very young age (five to 10 years) (27,28), and it was reported in an autopsy study that the extent of fatty streaks and even advanced lesions (fibrous plaques and plaques with calcification or ulceration) in the right coronary artery and abdominal aorta were associated with obesity and size of the abdominal panniculus (29). From a clinical point of view, it is important to note that maximal density of macrophages/mm² in atherosclerotic lesions is associated with visceral obesity (30), reduced coronary flow reserve related to body fat distribution and insulin resistance (31), and the MetS associated with lipid-rich plaque (32). In a systematic review and meta-analysis of longitudinal studies (33), it has been reported that individuals with the MetS are at increased risk of a cardiovascular events and death (relative risk 1.78). Recently, it was reported that a BMI within normal limits may confer additional risk of CHD as seen with moderately elevated BMI (21). These observations with regard to BMI have created uncertainty regarding the link between obesity and atherosclerosis and highlight some of the inherent limitations of BMI to predict adverse health outcomes. In contrast, WC and WHR may more accurately reflect the additional risk conferred by obesity, as published recently (21).

Coronary artery disease revascularization procedures in obesity

Cardiac surgeons often perceive obesity as a risk factor for perioperative adverse outcomes following coronary artery bypass surgery (CABG). The presences of comorbidities, as well as the technical difficulties inherent to the surgical and postsurgical care of obese patients, likely contribute to this perception. However, obesity has not been reported to be associated with increased mortality or postoperative cerebrovascular accidents following CABG in numerous studies (34,35). In contrast to BMI-defined obesity, the components of the insulin resistance syndrome have been associated following CABG, with angiographic progression of atherosclerosis in nongrafted coronary arteries (36). Finally, the MetS was reported to be a strong and independent risk factor for morbidity and mortality following CABG (37) as well as an increased risk of developing postoperative complications such as AF and renal failure (38). More recently, the MetS has also been documented as a risk factor for the development of aortic valve sclerosis and stenosis (39). Patients with features of the MetS had a faster progression of aortic stenosis and experienced more events, defined as aortic valve replacement or death (40), and experienced a twofold greater risk of developing dysfunction of an implanted aortic bioprosthesis (41).

TABLE 3
Functional and electrocardiographic changes that may occur in obese individuals

Functional
Left ventricular diastolic dysfunction
Left ventricular hypertrophy (eccentric, concentric)
Right ventricular hypertrophy
Pulmonary hypertension
Autonomic dysfunction
Arrhythmia, sudden death
Adipositas cordis (cardiomyopathy of obesity)
Electrocardiographic
Increased heart rate, QRS interval and/or corrected QT interval
False-positive criteria for inferior myocardial infarction

Clinical targeting of higher risk obesity

In postmenopausal women with established coronary artery disease from the Heart and Estrogen/progestin Replacement Study (HERS) (42), it was reported that both BMI and WC were associated with mortality, but WC may be more important than BMI. Indeed, for every category of BMI, mortality rates were higher for women whose WC was greater than 88 cm compared with those with a smaller WC. In contrast, for every category of WC, women with normal BMI had higher mortality than those who were overweight or obese (42). Thus, higher levels of baseline WC were associated with a 22% increased risk of mortality after adjusting for BMI and traditional risk factors. Additionally, after adjustment for WC, higher levels of baseline BMI were associated with a 20% decreased risk of mortality. Only women whose WC was less than 88 cm had a decreased risk of mortality with increasing BMI (42). In the Nurses' Health Study (43), WHR and WC were independently strongly associated with increased risk of coronary artery disease among women with a BMI of 25 kg/m² or less, and in the Paris Prospective Study (44), sagittal diameter (ie, abdominal obesity) was the only significant predictor of cardiac death. In patients with known CVD or following acute myocardial infarction, overall obesity as assessed by BMI was not associated with cardiovascular mortality, myocardial infarction and total mortality when abdominal obesity indexes (WHR and WC) were integrated into the statistical analysis (12,45,46). In the Trandolapril Cardiac Evaluation (TRACE) register, the mortality rate of abdominally obese men was increased 23% compared with men who were not abdominally obese (46). Additionally, a recent meta-analysis (47) of the influence of body weight or obesity measures in patients with coronary artery disease reported a better outcomes for cardiovascular and total mortality seen in overweight and mildly obese groups that could be due to the lack of discriminatory power of BMI to adequately reflect adiposity (47). This has been demonstrated in the study by Lakka et al (48) and encountered in other studies of over 50,000 Danish subjects (49,50). Because BMI measures total body mass (both fat and lean mass), after adjusting for WC, BMI may better represent the protective effect of lean body mass on mortality. This negative confounding may have been underappreciated in prior studies that did not adjust for measures of abdominal obesity.

Despite the high correlation between WC and BMI, the combination may be very relevant in clinical practice because WC for a given BMI was a strong predictor of all-cause mortality. Studies reporting negative results between all-cause mortality and WC did not mutually adjust WC and BMI, a possible explanation for the inconsistent results (51,52).

Guidelines for optimal weight in older individuals are limited by uncertainty about the ideal BMI (53). The excess health risk associated

TABLE 4
Benefits of weight reduction on the cardiovascular system

Benefits
Improvement of left ventricular diastolic dysfunction
Improvement of left ventricular systolic dysfunction
Decreased
Blood volume
Stroke volume
Cardiac output
Pulmonary capillary wedge pressure
Peripheral edema
Left ventricular mass
Resting oxygen consumption
Systemic arterial pressure
Filling pressures of the right and the left side of the heart
Systemic arterial resistance (or no change)
Resting heart rate
Corrected QT interval
Heart rate variability

with a higher BMI declines with increasing age. An explanation for the lack of a positive association with BMI and mortality at older ages is that, in older persons, BMI is a poor measure of body fat. Sarcopenic obesity, which is defined as excess fat with loss of lean body mass, is a highly prevalent problem in older individuals. The ideal BMI may be higher in older adults than in middle-aged adults. It was recently reported in approximately 4000 persons aged 75 years and older that WHR rather than WC predicted mortality in nonsmoking men and women, mainly because of the association with cardiovascular deaths (54). In the Health Professionals Study, in men 65 years and older, WC and WHR were significantly related to CVD mortality (51). It was found in the Cardiovascular Health Study of over 5000 patients 65 years of age or older with a mean BMI of 26.3 kg/m² (42% overweight) that higher BMI values indicated a lower mortality risk once the risk attributable to WC was accounted for, whereas WC values indicate a higher mortality risk once the risk attributable to BMI was accounted for (55). Death rates were highest in individuals with a high WC within the overweight and obese BMI categories. Finally, in a large case control study, WHR was found to be more strongly associated than was BMI with myocardial infarction, whereas the association with BMI was weak and intermediate for WC in older patients (56). To discriminate low-risk versus high-risk subjects, perhaps WHR would be more useful.

The introduction of WC as a simple risk measure in public health settings has already begun, but the simplification is under debate. Thresholds for WC to identify individuals with excess cardiovascular risk have been suggested but the choice of WC thresholds should be based on outcomes of importance, such as all-cause mortality or myocardial infarction (56). It seems from the data available that there is no basis for choosing thresholds because the mortality rate ratio increased steadily with WC. Nevertheless, there may be differences between different ethnic groups (56). From a clinical viewpoint, both indices should probably be assessed and may be useful to better define 'at risk' obesity because it was observed in the IDEA (International Day for the Evaluation of Abdominal obesity), which included 157,211 patients, that both WC and BMI were independently associated with the presence of CVD in both men and women (57). Nevertheless, with all the knowledge available in the literature regarding obesity and CVD, assessment and management of obesity following acute coronary syndrome is inadequate (58).

CONCLUSION

Improvement in risk factor recognition and management that developed through the last decades in modern cardiology might be counteracted by the greater incidence of obesity. There are numerous indices to evaluate obesity (BMI, WC, WHR) or body fat content (eg, bioelectrical impedance, hydrostatic weighing, dual energy x-ray absorptiometry, air displacement plethysmography). Accurate diagnosis of obesity may entail more refined assessment of body fat composition/distribution. Through the years, researchers have helped refine indices associated with CVD. For example, total cholesterol has been replaced by low-density and high-density cholesterol to better evaluate the patient's risk of CVD. We are no longer using total weight to appreciate the presence of obesity. Although BMI has been useful in epidemiological

studies to assess the presence of obesity, it fails to differentiate between differing body compositions. BMI does not characterize excess centrally distributed adiposity, which is more consistently associated with adverse effects on metabolism, dyslipidemia and insulin resistance. BMI also can be falsely increased in the presence of increased lean body mass (such as in trained athletes) and low BMI values are associated with chronic conditions leading to loss of lean body mass. Thus, other clinical indices of adiposity such as WC and WHR should be incorporated in the clinical approach of the cardiologist to better target and manage 'at risk' obesity.

CONFLICTS OF INTEREST: None.

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