Obesity and Cardiovascular Disease

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Obesity is a major contributor to the prevalence of cardiovascular disease in the developed world, and yet has only recently been afforded the same level of attention as other risk factors of coronary artery disease. Obesity is a chronic metabolic disorder associated with cardiovascular disease and increased morbidity and mortality. It is apparent that a variety of adaptations/alterations in cardiac structure and function occur as excessive adipose tissue accumulates, even in the absence of comorbidities. Shifts toward a less physically demanding lifestyle are observed today throughout different populations, and this scourge associated with obesity implicates a corresponding increase in the number of individuals afflicted with the metabolic syndrome, which defines the obese patient as being "at risk." Adipose tissue is not simply a passive storehouse for fat, but an endocrine organ that is capable of synthesizing and releasing into the bloodstream a variety of molecules that may impact unfavorably the risk factor profile of a patient. Indeed, obesity may affect atherosclerosis through unrecognized variables and risk factors for coronary artery disease such as dyslipidemia, hypertension, glucose intolerance, inflammatory markers, and the prothrombotic state. By favorably modifying lipids, decreasing blood pressure, and decreasing levels of glycemia, proinflammatory cytokines, and adhesion molecules, weight loss may prevent the progression of atherosclerosis or the occurrence of acute coronary syndrome events in the obese high-risk population.

Introduction

Calorie imbalance, in part due to excess calorie consumption, is related to a rising prevalence of obesity. Populations of industrialized countries are becoming more overweight as a result of changes in lifestyle, and obesity may well become the most common health problem of the 21st century [1,2,3•]. Obesity is a major contributor to the prevalence of cardiovascular disease (CVD) in the developed world, and yet has only recently been afforded the same level of attention as other risk factors of coronary artery disease (CAD).

It was recently stated by the Public Health Approaches to the Prevention of Obesity (PHAPO) working group of the International Obesity Task Force (IOTF) that "In every country in the world today, depending on its stage of epidemiologic transition, chronic non-communicable diseases such as CVD, cancer, diabetes, and osteoporosis are either newly appearing, rapidly rising, or already established at high levels" [3•]. Thus, obesity is a major contributor to the global burden of disease and disability because it is a risk factor for numerous medical conditions such as heart disease, diabetes, hypertension, stroke, pulmonary emboli, certain cancers, osteoarthritis, gallbladder disease, and respiratory abnormalities [1]. Indeed, deaths from noncommunicable diseases are expected to rise from 28.1 million to 49.7 million a year, an increase in absolute numbers of 77% [3•], and ischemic heart disease is predicted to become the leading worldwide cause of disease burden in 2020 (Table 1).

The Metabolic Syndrome

A high body mass index (BMI) is significantly associated with myocardial infarction, coronary insufficiency, and sudden death; the association seems strongest with sudden death [4]. Although, obesity per se is considered a major modifiable risk factor for ischemic heart disease [2], it is of importance to remember that a remarkable heterogeneity exists among obese subjects, and the presence of visceral obesity generally worsens the metabolic portrait that is associated with a cluster of traditional and nontraditional risk factors, which are all potentially synergistic and deleterious (Table 2). Because not all obese individuals are at increased risk of CVD, the challenge for the clinician is to screen the obese patients who are at risk (*ie*, the obese state associated with the metabolic syndrome). Using the criteria established by the National Cholesterol Education Panel (NCEP) [5••], the metabolic syndrome is defined as three or more of the following: 1) waist circumference for men greater than 102 cm and for women greater than 88 cm; 2) fasting triglycerides of 150 mg/dL or greater (≥1.7 mmol/L); 3) high-density lipoprotein (HDL) cholesterol less than 40 mg/dL (<1.0 mmol/L) for men and less than 50 mg/dL (<1.3 mmol/L) for women; 4) blood pressure greater than 130/85 mm Hg; and 5) fasting plasma glucose of 110 mg/dL or more (≥6.1 mmol/L). Presently, the "metabolic syndrome" is a working definition only, and it remains unclear as to whether the five components provide equal risk to the development of cardiovascular disease events.

Table 1. The five leading causes of disease burden worldwide as measured in disability-adjusted life years in the 1990s and the 2020s

1990s	2020s (predicted)
1. Lower respiratory infections	1. Ischemic heart disease
2. Diarrheal diseases	2. Unipolar major depression
3. Perinatal conditions	3. Road traffic accidents
4. Unipolar major depression	4. Cerebrovascular disease
5. Ischemic heart disease	5. Chronic obstructive disease

Adapted from Kumanyika *et al.* [3•].

There is ample evidence suggesting that the presence of excess fat in the abdomen in proportion to total body fat is an independent predictor of CVD [6–8], and the features of the metabolic syndrome are most often the consequence of an excessive accumulation of abdominal fat (especially when accompanied by a high accumulation of visceral adipose tissue) [9–13]. For instance, among equally overweight and obese individuals, patients with a high accumulation of visceral adipose tissue are characterized by disturbances in plasma glucose/insulin homeostasis; elevated triglycerides (TG) and apolipoprotein B concentrations; low HDL cholesterol levels; an increased proportion of small dense low-density lipoprotein (LDL) and small dense HDL particles; and by postprandial hyperlipidemia, reflecting a more saturated system for the clearance of TG-rich lipoproteins either of exogenous or endogenous origin [9-13]. This profile is also accompanied by a prothrombotic, inflammatory state [14–18]. Abdominal distribution of body fat is associated with increased plasma levels of fibrinogen, factor VII and factor VIIIc coagulant activities, and tissue plasminogen activator (tPA) antigen and plasminogen activator inhibitor I (PAI-I) antigen and activity [19–22]. This hypercoagulable state, which accompanies excessive central fat deposition, may also be associated with impaired endothelial function [23,24]. Therefore, the abdominally obese patient with the features of the metabolic syndrome is characterized by an atherogenic, prothrombotic, and inflammatory profile, which probably substantially increases the risk of an acute coronary syndrome [25].

From a pathophysiologic viewpoint, it is important to keep in mind that adipose tissue is not simply a passive storehouse for fat, but an endocrine organ that is capable of synthesizing and releasing into the bloodstream a variety of molecules [1]. Of clinical consideration, circulating concentrations of PAI-1, angiotensin II, C-reactive protein (CRP), fibrinogen, and tumor necrosis factor α (TNF-α) are all related to BMI [15,20]. It has been estimated that in vivo, approximately 30% of the total circulating concentrations of interleukin 6 (IL-6) originate from adipose tissue [15,26]. This is of importance because IL-6 modulates CRP production in the liver, and CRP may be a marker of a chronic inflammatory state that predisposes to acute coronary syndromes [27–30].

Thus, when obesity is associated with the metabolic syndrome, attention from the clinician is needed; this is not an uncommon relationship [31]. The metabolic syndrome was encountered in approximately 10% of subjects with normal glucose tolerance, approximately 50% of the subjects with impaired fasting glucose/impaired glucose tolerance, and approximately 80% of those with type 2 diabetes [32]. From an epidemiologic perspective, a recent report indicated that 20% to 25% of the adult US population has the metabolic syndrome [33••]. This is of concern because the magnitude of risk associated with insulin resistance (*ie*, the metabolic syndrome) may be of the same magnitude as that of hypercholesterolemia [34]. From a clinical point of view, abdominal obesity-associated metabolic syndrome can be assessed easily, at least in men. It was reported in men with a waist circumference greater than 90 cm and with triglycerides greater than 2.0 mmol/L that this may identify as many as 80% of the subjects with the insulin resistance syndrome; this is associated with a cluster of risk factors for CVD [9,35]. However, the waist circumference cutoff may lose predictive power in patients with a BMI of 35 kg/m^2 or more [36].

Atherosclerosis

An important early event in the development of atherosclerosis is endothelial cell dysfunction and inflammation of the vessel wall [37]. Atherosclerosis begins in childhood with deposits of cholesterol in macrophages and smooth muscle cells located in the intima of large muscular arteries to form fatty streaks [38,39]. As individuals age, fibrous plaques develop and progress to complicated lesions wherein hemorrhage or rupture may lead to acute coronary events [29,30].

In adults, obesity is often associated with advanced atherosclerosis. Indeed, examination of arteries postmortem from young individuals (15 to 34 years of age) who died from accidental injury, homicide, or suicide demonstrates that the extent of fatty streaks and raised lesions (fibrous plaques and plaques with calcification or ulceration) in the right coronary artery (RCA) and in the abdominal aorta were associated with obesity and abdominal panniculus [40–43]. The prevalence of obesity, defined as the thickness of panniculus adiposus and BMI

of 30 kg/m^2 or more, in the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) study was 14.3% [44•]. Obesity in young men, as defined by BMI, was associated with both fatty streaks and raised lesions in the RCA and with microscopic atherosclerosis and stenosis in the left anterior descending artery. Black subjects had more extensive fatty streaks than white subjects in all arterial segments, and men had more extensive raised lesions in the RCA than women [44•]. The prevalence of total atherosclerosis (fatty streaks and raised lesions) in the RCA increased from approximately 60% in the youngest age group (15 to 19 years) to greater than 80% in men and approximately 70% in women in the oldest age group (30 to 34 years) [44•]. There was a 5% increase in arterial surface involved with lesions for each 5-year age increase [44•]. Importantly, when BMI and panniculus thickness were used together in males, a BMI of 30 kg/m^2 or more was associated with RCA raised lesions only within the higher (≥17 mm) classification of panniculus thickness, reinforcing that central fat distribution is more important than total fat as a risk for CVD [44•]. Lesion prevalence was greatest in the first 2 to 3 cm of the RCA, and in men the effects of adiposity on raised lesions in this region were evident even before the age of 25 years [45••]. Moreover the association between adiposity and RCA lesions after adjusting for other risk factors, namely non-HDL and HDL cholesterol concentration, hypertension, smoking, and glycohemoglobin, was still statistically significant; these risk factors accounted for only 15% of the effects on atherosclerosis [45••]. On the other hand, there was little association of adiposity with coronary atherosclerosis in young women, with a nonsignificant trend for an association between BMI and fatty streaks in women who presented a thick panniculus adiposus [45••]. Of note, however, raised lesions in coronary arteries in young women lag behind those in young men by about 10 years, independently of risk factor status [45••]. The same parallel probably applies to postmenopausal women, who often present with clinically significant atherosclerosis 10 years later than men. In the proximal left anterior descending (LAD) artery, obesity and hypertension were associated with grade 4 and 5 lesions, which were defined as raised or advanced lesions with necrotic lipid cores that may be clinically significant [44•,46]. These data provide evidence that obesity in adolescents and young adults accelerates the progression of atherosclerosis decades before clinical manifestations appear. Thus, the control of childhood obesity is justified for the prevention of CVD as well as other chronic disease associated with it.

Although the relationship between obesity and atherosclerosis is often dependent on obesity-related comorbidities (*eg*, hypertension, glucose intolerance, and dyslipidemia), after a follow-up of 26 years, the Framingham Heart Study [47] and the Manitoba Study [4] have both documented that obesity is an independent predictor of CVD, particularly among women. This association was more pronounced in individuals younger than 50 years of age, reinforcing the idea that obesity leads to premature atherosclerosis. There is evidence, however, that dyslipidemia, smoking, obesity, and hyperglycemia are related to fatty streaks in the second decade of life, and the same risks factors, along with hypertension, are associated with plaques in the third decade of life [40]. Hence the American Heart Association has stated that obesity is a major modifiable risk factor, rather than independent risk factor, for atherosclerotic cardiovascular disease [2,48].

Childhood Obesity and the Development of Cardiovascular Disease

Childhood obesity has reached epidemic proportions. During the past three decades, the number of overweight children in the United States has more than doubled. In 1983, 18.6% of preschool children in the United States were defined as overweight and 8.5% were defined as obese, whereas in 2000, 22% of preschool children were overweight and 10% were obese [49]. Similar increases in the prevalence of obesity have been observed worldwide [50]. Obesity has a substantial influence on the cardiovascular system [1], and it is of importance to recognize that childhood obesity is directly linked to abnormalities in risk profile of both CAD and diabetes [51]. Indeed, over 40 years ago it was suggested that atherosclerosis was at least in part a pediatric nutrition problem [52]. Because modification of risk factors should occur before the ages when the effects of atherosclerosis are observed, simple risk factor modification (including diet, physical activity, and weight control) should begin early in life, at least by the late teens [53]. This has been recently demonstrated by the observations that the secular trend toward obesity in children is accompanied by detrimental risk factors for the eventual development of CVD [54••,55].

Coronary Artery Disease and Revascularization Therapy

The metabolic syndrome should probably be treated aggressively following revascularization therapy. Indeed, abnormal glucose tolerance may be an important determinant for long-term prognosis after coronary angioplasty [56]. Moreover, following coronary artery bypass graft (CABG), the components of the metabolic syndrome are associated with angiographic progression of atherosclerosis in nongrafted coronary arteries [57].

The cardiac catheterization laboratory at Duke University has observed an increase in obesity from 20% to 33% in over 9000 patients studied between 1986 and 1997 [58]. Although obesity was associated with younger age, comorbidities, and only single-vessel disease at baseline [58,59], obesity was associated with more clinical events during the post–30-day period after cardiac catheterization [58]. In another study [59], obesity was associated with higher

cumulative in-patient medical costs and significant differences in unadjusted survival at 10 years [58]. This was not true in the study of Gruberg *et al*. [59].

Coronary Artery Bypass Graft

Rightfully, surgeons often quote obesity as a risk factor for perioperative morbidity and mortality. The presence of comorbidities like hypertension, CAD, dyslipidemia, and type 2 diabetes mellitus, as well as the technical difficulties inherent to the surgical and postsurgical care of obese patients, likely contribute to this perception. Obese patients have been shown to have a higher incidence of postoperative thromboembolic disease in noncardiac surgery, and the high risk of thromboembolic disease in obese patients may necessitate an aggressive approach to deep venous thrombosis prophylaxis [60]. In contrast to frequent beliefs, obesity is not associated with increased mortality or postoperative cerebrovascular accidents following CABG. There is, however, an increased risk of sternal and superficial wound infection, saphenous vein harvest site infection, and atrial dysrhythmias in obese patients undergoing bypass surgery [61,62].

Clinical Trials and Cardiovascular Disease Outcome in Patients with Obesity

There is some evidence that patients with obesity and/or the metabolic syndrome with coronary heart disease (or with coronary heart disease risk) may respond better to lipid-modifying interventions in clinical trials. In the Helsinki Heart Study [63], men with hypercholesterolemia with a BMI greater than 26 kg/m^2 and either hypertriglyceridemia plus low levels of HDL cholesterol and/or three to four additional risk factors for coronary heart disease appeared to respond better to the gemfibrozil intervention than patients without obesity. Moreover, in patients with coronary heart disease and baseline levels of HDL cholesterol less than 40 mg/dL, the metabolic syndrome predicted a superior reduction in coronary heart disease events with gemfibrozil [64]. Whether this relative benefit of obese patients with or without the metabolic syndrome extends to other cardiovascular disease risk factors remains unexamined, but it is clearly worthy of additional attention.

Conclusions

Obesity is a chronic metabolic disorder associated with CVD and increased morbidity and mortality. It is apparent that a variety of adaptations/alterations in cardiac structure and function occur as excessive adipose tissue accumulates, even in the absence of comorbidities. Large shifts towards a less physically demanding lifestyle are observed today throughout different populations, and this scourge associated with obesity implicates a corresponding increase in the number of individuals afflicted with the metabolic syndrome. This deleterious trend endangers the advances made in reducing morbidity and mortality from CVD over the past two decades [65]. It also poses a challenge to physicians to modify their practice to place more emphasis on lifestyle changes [53]. More prevalent cardiac risk factors in obese and very obese CAD patients at baseline seemed to counteract potential survival benefits derived from the younger age and less extensive CAD of these individuals. Consequently, the long-term clinical burden of illness is greater [58]. Of note, the impact of excess body fat on mortality is delayed and may not be seen in short-term studies [58] compared with other ones [25,28,45••,47]. Indeed, cardiovascular mortality assessed in 3606 subjects with a median follow-up of 6.9 years was increased substantially in subjects with the features of the metabolic syndrome (12.0% vs 2.2%) [32], and it was shown recently that abdominal obesity is associated with increased risk of acute coronary events in men [28].

Obesity may affect atherosclerosis through risk factors like dyslipidemia, hypertension, glucose intolerance, inflammatory markers, and the prothrombotic state. Many of these are components of insulin resistance. Although there are no prospective studies to date demonstrating that weight loss increases survival, there is strong evidence that weight loss in "at risk" overweight and obese individuals reduces the incidence of diabetes [66,67], and because diabetes is a CAD equivalent, probably CVD as well. By favorably modifying lipids and by decreasing blood pressure, levels of glycemia, proinflammatory cytokines (*ie*, TNF-α, IL-6, CRP) [68–70], and adhesion molecules (*ie*, P-selectin, circulating inter-cellular adhesion molecule-1, vascular adhesion molecule-1) [68], weight loss may prevent the progression of atherosclerosis or the occurrence of acute coronary syndrome events. Moreover, weight loss translates into improvement in endothelial function [68].

If the current worldwide epidemic of childhood obesity cannot be averted, its full public health impact will be felt in the contemporary cardiology world as affected children become adults and the long-term complications of obesity develop. The best way to treat a disease is to prevent it. For obesity, this is where the emphasis needs to be placed.

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