Obesity and Cardiovascular Disease

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INTRODUCTION

The physical, medical, economic, and societal impact of the obesity epidemic is already staggering, and it will dramatically affect future generations.[1] Obesity is associated with an increased risk of developing metabolic syndrome, diabetes mellitus, hypertension, fatty liver, cholelithiasis, obstructive sleep apnea, osteoarthritis, polycystic ovarian disease, and several types of cancer. Many of these problems are discussed in other articles in this symposium, and Dr. Alan Peterson has authored an extensive discussion of the metabolic syndrome that will appear in a future issue.

The most worrisome long-term effect of obesity is the associated increase in atherosclerotic cardiovascular disease (ASCVD) and its inherent physical consequences.[2,3] With the continuing increase in the number of overweight and obese individuals, it is important to understand these cardiovascular consequences and to implement evidence-based strategies to prevent obesity-related heart disease and to increase life expectancy.

THE METABOLIC SYNDROME & CARDIOVASCULAR DISEASE

The metabolic syndrome is a term used to define the sum of risk factors that predispose individuals to atherosclerotic cardiovascular disease. The clinical diagnosis is made when a patient has three or more of the risk factors outlined below.

Waist Circumference	
Men	>102 cm (>40 in)
Women	>88 cm (>35 in)
Triglycerides	≥150 mg/dl
HDL Cholesterol	
Men	<40 mg/dl
Women	<50 mg/dl
Blood Pressure	≥130/≥85 mm Hg
Fasting Glucose	≥100 mg/dL

Visceral adiposity in the omental and paraintestinal regions (the so-called "apple-configuration") is a strong risk factor for the development of hypertension, dyslipidemia, coronary artery disease, and the insulin resistance of Type 2 diabetes mellitus (DM).[5] Unlike peripheral fat cells, visceral fat cells are more resistant to the effects of insulin and more sensitive to lipolytic hormones, leading to an increase in the release of free fatty acids and providing a greater substrate for hepatic triglyceride synthesis. The increased triglyceride levels are followed by decreasing levels of cardioprotective HDL and Apo A. Though the serum levels of total cholesterol and LDL might not always rise to an appreciable degree, this insulin resistant dyslipidemic state causes significant increases in the concentrations of strongly atherogenic Apo B and small, dense LDL particles.[6]

Additionally, visceral adipose tissue becomes an endocrine organ that releases into the bloodstream a variety of peptide and nonpeptide compounds that play a role in vascular homeostasis. Among the more clinically relevant is elevated C-reactive protein (CRP) through increased production of Interleukin-6 (IL-6), fibrinogen, factor VII, factor VIII, tumor necrosis factor-α, adiponectin, leptin, plasminogen activator inhibitor (PAI) and decreased levels of antithrombin III.[1,5] The composite effect of these compounds is a chronic inflammatory, prothrombotic, and proatherogenic state, whose end result is coronary, cerebral, and peripheral vascular disease.

Obesity, and particularly visceral obesity and the metabolic syndrome, actively promote biochemical and neurohormonal processes that are, both directly and indirectly, injurious to vascular health and increase the risk of atherosclerotic cardiovascular disease.[1,3,5,6]

HYPERTENSION

Obesity increases the risk of developing hypertension (HTN), which is a strong risk factor for atherosclerotic cardiovascular disease, left ventricular hypertrophy (LVH), heart failure, chronic renal failure and cerebrovascular accident (CVA). A 10-kg weight gain is associated with an increase of 3.0 mm Hg in systolic and 2.3 mm Hg diastolic blood pressure, which translates to a 12% increased risk for ASCVD and a 24% increased risk for CVA.[7]

The development of obesity-induced hypertension is multifactorial and includes an increase in peripheral

vascular resistance via endothelial dysfunction, activation of the sympathetic nervous system, direct and indirect renal effects, sleep apnea, and other vasoactive effects of peptides released from adipocytes.[1,3]

The hemodynamic changes that occur in obesity are a direct consequence of the increased blood flow needed to perfuse adipocytes. With increasing mass, there is a concomitant increase in oxygen demand which is initially supplied by a compensatory increase in cardiac output. This leads to a high output state with increased blood volume, stroke volume and cardiac output. The left ventricular chamber dilates to accommodate the increasing volume and usually develops an eccentric type of hypertrophy. The left atrium (LA) also enlarges in response to the increased venous return and blood volume. With time the left ventricular hypertrophy and diastolic dysfunction may contribute to increasing LA size. These morphologic changes are initially necessary but eventually the diastolic function and the initial hyperdynamic systolic function worsen, culminating in heart failure.[1]

There is also some evidence to suggest a correlation between insulin resistance and hypertension. The Normotensive Aging Study showed that urinary norepinephrine levels are increased with increasing BMI, abdominal girth, and insulin-glucose levels.[9]

Obesity is associated with an increase in both oxidative stress and the proinflammatory effects of certain cytokines. Interleukin-6 is produced in adipocytes, and increasing adipocyte mass causes an elevated production of IL-6.8 These higher levels of IL-6 subsequently stimulate production of CRP in the liver and both play a role in endothelial dysfunction by decreasing nitric oxide (NO), leading to vasoconstriction and increasing vascular resistance.[1,8]

Leptin is a hormone produced primarily by white adipose tissue that regulates energy intake and expenditure as well as being critically involved in appetite suppression. Leptin signals the brain when the body has had enough caloric intake and obese patients tend to have a resistance to leptin and thus do not feel satiety. These leptin-resistant patients ultimately have elevated leptin levels, which have other untoward effects and stimulate the hypothalamus to increase blood pressure through activation of the sympathetic nervous system.[6,10]

CORONARY ARTERY DISEASE AND OBESITY

Obesity is a predictor of coronary artery disease both as an independent factor and as a progenitor of the multiple atherogenic processes of the Metabolic Syndrome. This phenomenon has been noted in the Framingham Heart Study, the Manitoba Study, and the Harvard Public Health Nurses Study. In the Framingham Study, patients 28-62 years of age were followed for 26 years. Among patients younger than 50, the heaviest group experienced twice the incidence of coronary artery disease as the lean group. After adjusting for other cardiovascular risk factors, the risk for obese women of the same age group was 2.4 fold greater than the lean women.[11]

Even more worrisome is that an elevated BMI in childhood is associated with an increased risk of heart disease in adulthood.[12] An autopsy study in individuals 15-34 years of age who died of non-cardiac causes revealed that the extent of fatty streaks and complex advanced lesions (fibrous, ulcerated, or calcified plaques) in the right coronary artery and the abdominal aorta were associated with obesity and the size of the panniculus. This association remained significant even after adjusting for other risk factors (non-HDL, HDL, smoking, hypertension, and glycohemoglobin). These data lead to the ominous realization that obesity in adolescents and young adults accelerates the progression of atherosclerosis decades before the onset of clinical symptoms.[1,14] Just as visceral adiposity is an important risk factor for the development of premature coronary artery disease in adolescents, the process of abdominal fat deposition after menopause may partially explain why the increased risk of ASCVD in women occurs 10-20 years later than men.[13]

HEART FAILURE

Heart Failure in obesity is multifactorial. Systolic and diastolic dysfunction are caused by 1) the ischemic effects of coronary artery disease, 2) the usually eccentric but at times concentric LVH caused by hypertension, 3) the increase in LV dilatation caused by an increased stroke and blood volume and cardiac output, and 4) the contribution of RV dysfunction from sleep apnea and pulmonary hypertension. Combined with fatty infiltration of cardiomyocytes, these effects lead to a form of apoptosis and subsequent left ventricular dysfunction.

With the increased incidence and prevalence of congestive heart failure (CHF), associated mortality rates are climbing. Despite new pharmacologic and device therapies, the 5-year survival rate for CHF is estimated at 50%. The risk of CHF increases 5% for men and 7% for women for each increment of BMI, representing a linear increase which does not plateau. The finding that ejection fractions of <40% are seen in 42% of obese as compared to 54% of normal-weight patients with heart failure confirms that diastolic heart failure is the more common type of dysfunction among the obese.[1]

Interestingly, CHF patients with higher BMIs are at decreased risk of death and recurrent hospitalization when compared to those with normal BMIs.[6,15] This "Obesity Paradox" is the subject of ongoing investigation and debate. Patients in

advanced heart failure tend to be in a chronic catabolic state and some researchers postulate that obese patients, by virtue of their weight, have a higher metabolic reserve. Obese patients have lower levels of circulating atrial natriuretic peptides, with attenuated sympathetic nervous systems and renin-angiotensin responses. These characteristics confer a better prognosis.

Finally, because obese patients have hypertension, the elevated pressures may allow them to tolerate higher levels of cardioprotective medications and thus obtain greater therapeutic benefit from these agents.[6,16,17] Despite the perceived "cardio-beneficial" effects of obesity in heart failure, it is important to remember that with or without heart failure, a higher BMI is independently associated with higher mortality.

ARRHYTHMIAS

"Sudden Death is more common in those who are naturally fat than in the lean."

Hippocrates[18]

Visceral adiposity and obesity have complex effects on the cardiac conduction system. Even in the absence of left ventricular dysfunction, there is a significant increase in the incidence of sudden cardiac death and arrhythmias in obese patients. In the Framingham Study, sudden cardiac death was 40 times higher in the obese cohort.[19] There is a strong correlation between increased BMI and prolonged QTc.[20]

Several mechanisms account for these associations: 1) increased free fatty acids, which are plentiful in obese patients, may affect depolarization; 2) an increase in plasma catecholamines may decrease the threshold for arrhythmias particularly in patients with obesity-associated cardiomyopathy;[21] 3) elevated glucose concentrations may cause an increase in vasomotor tone and a decrease in nitrous oxide (NO) availability, thus increasing ventricular irritability;[22] 4) the autonomic nervous system and obesity are closely related. A 10% increase in body weight is accompanied by a decline in parasympathetic tone and heart rate modulation, which leads to an increase in heart rate and decreased heart rate variability, both factors contributing to increased mortality.[23]

Atrial fibrillation (AF) is the most common dysrhythmia in obesity and is associated with significant morbidity and mortality. Obese men and women are significantly more likely than the general population to develop AF (men - 52%; women - 76%). Obese patients with paroxysmal AF are more likely to progress to permanent AF which leads to a 3-5 fold increase in the risk of stroke and a 2-fold increase in risk of death.[24]

There are multiple causes for the increased incidence of AF in the obese population. Diastolic dysfunction from long-standing hypertension leads to concentric or eccentric left ventricular hypertrophy with associated transmural stresses and ultimate left atrial (LA) enlargement. Other structural changes include LV dilatation, which can subsequently lead to mitral regurgitation and LA enlargement, further worsening risk. Other contributing mechanisms are the effects of systemic inflammation and sleep apnea with associated autonomic imbalances and hypoxic periods.

Finally, in obese patients a metaplastic, not infiltrative, phenomenon occurs in the heart causing a significant increase in fat content within the tissue. Various tissues such as the sinus node, atrioventricular node, right bundle branch, and the myocardium at the atrioventricular ring are replaced by fat cells. The end result is a constellation of conduction defects like sinoatrial block, bundle branch block, and rarely, atrioventricular block. Irregular bands of adipose tissue may also cause pressure-induced atrophy of adjacent myocardial cells and secrete adipokines that may be injurious to normal myocytes. The high levels of triglycerides in these patients can also cause lipotoxic-induced cell dysfunction.[25]

EFFECTS OF WEIGHT LOSS

Effective and permanent weight loss is a difficult process with a known compliance rate of only 20% after one year. Even though dramatic lifestyle changes are most beneficial in those with only mild obesity (BMI 27-30), the cardiovascular and metabolic benefits will be seen among all obese patients.[26] The cardiovascular benefits of weight loss include decreases in blood volume, stroke volume, cardiac output, pulmonary capillary wedge pressure, LV mass, resting oxygen consumption, BP, cardiac filling pressures, resting heart rate, and QTc interval. Systolic and diastolic functions improve, heart rate variability increases, and there is no change in systemic vascular resistance.

Along with the cardiovascular benefits, there are significant metabolic changes that occur with weight loss leading to a decrease in overall morbidity and mortality. Lifestyle changes may lead to a 60% risk reduction in the development of diabetes mellitus and up to a 37% decrease in the prevalence of the metabolic syndrome.[7] Beneficial changes include decreased blood sugar, lipids, C-reactive protein, and prothrombotic and proatherogenic factors. These changes along with increased adiponectin levels and insulin sensitivity lead to a subsequent decrease in cardiac events and mortality.[27]

The advent of bariatric surgery has added a new tool to the limited armamentarium of weight loss options. Bariatric surgery has been shown to aid and accelerate the long-term benefits of weight loss by resolving Type 2 DM in up to 87% of patients and resolving obstructive sleep apnea in more than 85% of patients.28 Finally, mortality due to coronary heart disease was reduced by 56% and persisted as a continued risk reduction of 29% for up to 10 years.[29]

CONCLUSION

Obesity is an independent predictor of all-cause mortality in men and women. The vascular anatomic changes that eventually become clinical disease begin in obese children and adolescents, and the focus of more aggressive preventive measures must be on the young. The multiple and ever increasing deleterious effects of obesity create a self-perpetuating cycle of clinical illness and disability that eventually confines its victims to a non-productive life of existence only. These are the end results of the natural history of this tragic epidemic.

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