Obesity Cardiomyopathy: Pathophysiologic Factors and Nosologic Reevaluation

Samit Bhatheja, MD, MPH, Hemang B. Panchal, MD, MPH, Hector Ventura, MD and Timir K. Paul, MD, PhD

ABSTRACT

Cardiovascular disease in populations with obesity is a major concern because of its epidemic proportion. Obesity leads to the development of cardiomyopathy directly via inflammatory mediators and indirectly by obesity-induced hypertension, diabetes and coronary artery diseases. The aim of this review article is to re-visit the available knowledge and the evidence on pathophysiologic mechanisms of obesity-related cardiomyopathy and to propose its placement into a specific category of myocardial disease.

Key Indexing Terms: Obesity cardiomyopathy; Obesity paradox; Heart failure; Metainflammation. **[Am J Med Sci 2016;352 (2):219–222.]**

INTRODUCTION

Cardiovascular diseases are the number one cause of mortality in the United States,[1] which is undoubtedly related to consequences of epidemic obesity.[2] The association between these 2 major health enemies is well known.[3] The aim of this review article is to re-visit the available knowledge and the evidence on pathophysiologic mechanisms of obesity-related cardiomyopathy and to propose its placement into a specific category of myocardial disease.

PATHOPHYSIOLOGIC MECHANISMS

Obesity cardiomyopathy is a complex interplay of direct and indirect pathophysiologic factors related to obesity. Obesity is an independent risk factor for coronary artery disease (CAD), and is strongly associated with hypertension (HTN) and diabetes mellitus (DM), which indirectly leads to the development of ischemic, hypertensive and diabetic cardiomyopathy, respectively.[4-6] It is difficult to entirely separate out individual pathways of the so-called "direct mechanisms" owing to the complex interplay of the multiple pathophysiologic factors of obesity-related cardiomyopathy. Broadly, the direct factors classified as toxic or inflammatory mediators or as both,[4] metabolic and endocrinal factors and hemodynamic factors, all directly influence the structure and function of the myocardium leading to the development of cardiomyopathy, independent of classical cardiovascular risk factors.[4] Duration and severity of obesity are important deterministic factors for functional and structural derangements of the cardiovascular system.[7] Table 1 lists the adverse effects of obesity on cardiovascular and neurohumoral systems.[5,8-13] The examples of toxic mediators are free fatty acids, toxic lipid derivatives such as diacylglycerol, toxic nitric oxide metabolites and inflammatory mediators, which involve high-sensitivity C-reactive protein, cytokines, chemokines, macrophages, tissue necrosis factor α, etc.

OBESITY AND METAINFLAMMATION

Excess nutrient-induced derangement of inflammatory mediators is the basis of obesity-induced "metainflammation," a chronic low-grade inflammatory state.[14] This state can lead to multiorgan dysfunction gradually but in a similar manner as seen with acute inflammatory states like systemic inflammatory response syndrome.[5] Myocardial dysfunction caused by metainflammation is a result of direct injury through inflammatory mediators as well as due to dysfunction of other organs caused by metainflammation.

OBESITY AND INSULIN RESISTANCE

Obesity is a state of insulin resistance in which the excess adipose tissue release increases the number of macrophages, which in turn increase the levels of cytokines and chemokines affecting insulin sensitivity and subsequently insulin resistance.[15] High levels of tissue necrosis factor α leads to the downregulation of release of adiponectins, the absence of which leads to worsening of insulin resistance.[4,16] Additionally, insulin resistance leads to decreased glucose uptake and promotes the use of fat as a prime source of energy in cardiac myocytes. Higher toxic by-products of fat oxidation, such as diacylglycerol and ceramide and oxidative stress in cardiac myocytes leads to mitochondrial dysfunction, apoptosis and loss of functional myocardium.[9] Pathologically increased fat accumulation in functional cardiac myocytes induces the development of "cardiac steatosis," a state of cardiac myocyte hypertrophy and interstitial fibrosis associated with both diastolic and systolic dysfunction.[9-11] Insulin resistance also leads to a state of insulin excess

TABLE 1. Adverse effects of obesity on cardiovascular and neurohormonal systems.[5,8-13]

Left ventricle	Left ventricular hypertrophy and diastolic dysfunction due to systemic overload and effect of circulating cytokines and chemokines
	Left ventricular dilatation and systolic dysfunction due to myocardia scarring from "cardiac steatosis"
Right ventricle	Right ventricular hypertrophy due to elevated pulmonary arterial pressure and direct effect of circulating cytokines and chemokines on myocardium
	Right ventricular dilatation and failure due to significant rise in pulmonary vascular resistance
Vascular system	Systemic circulation
	Hypertension caused by higher sympathetic drive from higher circulating angiotensinogen levels
	Increased total blood volume
	Coronary circulation
	Accelerated atherosclerosis due to dyslipidemia and high leptin levels
	Pulmonary circulation
	Elevated pulmonary capillary wedge pressure due to left ventricular dysfunction or obesity hypoventilation syndrome or obstructive sleep apnea
	Elevated pulmonary arterial pressure
Neurohormonal system	Insulin resistance caused by downregulation of adiponectin from higher TNF-α levels
	Pancreatic β-islet cell apoptosis
	Hypothalamic inflammation

TNF, tumor necrosis factor.

binding to insulinlike growth factor receptors on myocardial cells and acting as a potent growth stimulator leading to myocardial hypertrophy. This abnormal hypertrophy and scarring of the myocardium leads to structural as well as functional loss of myocardial cells, contributing to obesity-induced cardiomyopathy. The insulin resistance is a contributing factor for glucose intolerance, metabolic syndrome and DM. Collaborative analysis of prospective studies showed a 5-fold increase in prevalence of diabetes as body mass index (BMI) increases from 15-50 kg/m^2.[17] Insulin resistance further deteriorates DM, which is already prevalent among individuals with obesity due to pancreatic β-islet cells apoptosis from chronic inflammation from obese state. The diabetic heart shows increased expression of angiotensin II receptors as well as impaired calcium homeostasis affecting endothelial dysfunction and leading to microvascular disease and the development of diabetic cardiomyopathy,[9] which contributes to obesity-induced cardiomyopathy. Furthermore, being a CAD equivalent, diabetes predisposes patients to accelerated atherosclerosis and CAD, leading to ischemic cardiomyopathy contributing to obesity-induced cardiomyopathy.

OBESITY AND ATHEROSCLEROSIS

When BMI is greater than 25 kg/m^2, every 5 kg/m^2 increase in BMI is associated with 40% higher mortality from ischemic heart disease.[11] The chronic inflammatory state of obesity results in structural and functional changes in the liver with increased release of high-sensitivity C-reactive protein, leading to accelerated atherosclerosis.[18] Obesity is a condition of high leptin levels as well as leptin resistance, which leads to increased atherosclerosis via toxic nitric oxide metabolite–mediated endothelial dysfunction, low high-density lipoprotein cholesterol level via promotion of hepatic uptake and high propensity of vascular thrombosis, which all contribute further to the development of CAD.[19] Studies demonstrated strong association between obesity and non-ST segment elevation myocardial infarction at young age.[20] CAD leads to systolic dysfunction, also known as "ischemic cardiomyopathy," which further contributes to obesity-induced cardiomyopathy.

OBESITY AND HTN

Endocrine dysfunction in patients with obesity includes not only insulin resistance but also elevated levels of adipose tissue–derived angiotensinogen, which is linked to pathologic remodeling of myocardium in similar fashion as in congestive heart failure. High angiotensinogen levels and high sympathetic drive due to low adiponectin levels lead to HTN that is already prevalent among individuals with obesity.[12,13] Every 5 kg/m^2 increase in BMI is associated with 5 mm of Hg rise in systolic blood pressure and 4 mm of Hg rise in diastolic blood pressure.[11] As part of metainflammation in obesity, involvement of hypothalamus leads to further worsening of HTN.[5] Over the period, HTN, if left untreated, leads to concentric left ventricular hypertrophy, the most common cause of diastolic dysfunction and to the development of hypertensive cardiomyopathy that further leads to obesity-related cardiomyopathy. The resulting increased myocardial mass places individuals with obesity at risk of supply demand mismatch, leading to further worsening of ischemia contributing to obesity cardiomyopathy.