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Obesity and Heart Failure as a Mediator of the Cerebrorenal Interaction

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Abstract

The obesity epidemic is contributing substantially to the burden of cardiovascular disease including heart disease and congestive heart failure, in the United States and the rest of the world. Overnutrition as a driver of obesity, promotes alterations in fatty acid, lipid, and glucose metabolism that influence myocardial function and progression of heart failure from diastolic to systolic failure. The association of progressive heart failure and progressive chronic kidney disease is well documented and often referred to as the cardiorenal syndrome, as well as a prognosticator for cerebrovascular disease (e.g. stroke). Whether the relationship between obesity, heart disease/failure and risk for chronic kidney disease and stroke is direct or a confluence of risk factors is poorly understood.

The increasing prevalence of obesity in the United States and the rest of the world is contributing to our substantial burden of cardiovascular disease including heart disease and congestive heart failure [1–4]. Overnutrition, with our Western diet as a driver of obesity, contributes substantially to a prooxidative/inflammatory milieu that promotes alterations in fatty acid, lipid, and glucose metabolism that influence myocardial function and progression of heart failure from diastolic to systolic failure [5]. Progressive heart failure is well documented to be associated with progressive chronic kidney disease (CKD), often referred to as the cardiorenal syndrome (CRS), as well as a prognosticator for cerebrovascular disease (e.g. stroke) [2–4] (fig. 1). Whether the relationship between obesity, heart disease/failure and risk for CKD and stroke is direct or a confluence of risk factors is unknown.

Recent data derived from the National Health and Nutrition Examination Survey (NHANES) support that incident and prevalent obesity in the United States is increasing [1–5]. In the context of cardiovascular disease, obesity has had a disproportionate impact on the adolescent and African-American communities and is thought to contribute annually to approximately 112,000 preventable deaths [6]. In this context there is substantial evidence to support a causal association between obesity and risk for cardiovascular disease (CVD) [7–9]. Data derived from the Framingham and Nurse's Health Study support a continuous, graded relationship between increases in BMI and mortality that began at an approximate BMI >25 as a marker for overweight or obesity [7, 8]. Another report from an Italian cohort

suggests a similar relationship between BMI, waist circumference and incident CVD events and all-cause mortality over a 10-year period [9]. Data from this study further suggest that the relationship between BMI and CVD mortality is independent of other metabolic markers such as blood pressure, dysglycemia, serum cholesterol, and triglycerides. Considering that overnutrition conveys this metabolic milieu, a recent meta-analysis further refines this relationship between obesity and CVD and suggests that BMI is an independent risk factor for coronary heart disease [10]. The authors suggest that the confounding elevations in cholesterol and blood pressure introduced in the individual studies may not completely explain the increased risk of heart disease and other comorbidities associated with obesity.

In this regard, obesity predisposes individuals to a large number of comorbidities and increased mortality rates. The risk for coronary heart disease and congestive heart failure (CHF) is clear and recent work highlights an even more complex relationship between obesity, stroke and kidney disease.

Obesity and Risk for CHF

Overnutrition and the development of overweight and obesity is associated with the development of insulin resistance, elevations in blood pressure, dysglycemia, oxidative stress, increased systemic inflammation and alterations in lipids that affect cardiac structure and ultimately function. However, excess body weight in-and-of-itself has been shown to increase both pre- and afterload volume retention, and affect peripheral arterial resistance that enhances pressor-dependent increases in left ventricular (LV) hypertrophy [11]. In turn, the impact that overweight and obesity has on cardiac function has been hard to separate from the elevations in blood pressure, as both eccentric and concentric LV geometric patterns have been described in these conditions that precondition the heart to fail (e.g. CHF) [11, 12].

The evolution of heart failure has been an area of extensive study, but in the context of obesity the pathological factors are incompletely understood. However, the graded risk between increasing obesity and CHF is well recognized and several studies over time have extended our understanding between the association of obesity and heart failure to longitudinal risk [7]. An analysis of 5,881 participants in the Framingham Heart Study, suggests a strong relationship between increases in BMI and an increased risk for heart failure. Following clinical adjustments for diabetes, hypertension, and lipids, for each incremental increase of 1 in BMI, there was 5 and 7% increase in risk for heart failure in men and women, respectively [13]. Preclinical data would suggest the early geometric changes in cardiac structure due to obesity pre-dispose to LV diastolic dysfunction and more recently, data from a Turkish cohort suggest that BMI is an independent predictor of LV diastolic dysfunction [14].

Changes in Myocardium Structure Related to Obesity

Obese individuals tend to have increased LV mass and wall thickness [15]. Our understanding of the effect that obesity has on the myocardial structure and function has evolved overtime. In the early part of 19th century, investigators attributed obesity associated increased weight of heart to epicardial fat deposition. Contrary to this, now it is

evident that increased heart weight is largely due to left ventricular hypertrophy. While subject to some controversy, it is generally thought the maladaptive LV structural changes progress with increasing duration and severity of obesity. Initially, the left ventricle undergoes concentric remodeling, which progresses to concentric hypertrophy and ultimately to eccentric hypertrophy if the stress of obesity continues unabated [16]. The progression has been challenged as some have reported a high prevalence of concentric hypertrophy; however, it is unclear if these findings are due to confounding factors like systemic hypertension [15]. Considering that obesity and hypertension coexist and that hypertension is underdiagnosed and often diagnosed late, it will be challenging to design epidemiological studies to answer this question with precision.

Pathogenesis of Metabolic Cardiomyopathy

In states of obesity and chronic over nutrition, the capacity of adipocytes to safely store fat is often exceeded. This leads to hypertrophy and hyperplasia of adipocytes as well as increased fat deposition in the myocardium. Adipocyte hypertrophy is considered a high stress state for the endoplasmic reticulum, and is associated with local hypoxia and pro-inflammatory changes like release of macrophage chemoattractant proteins and infiltration by macrophages [16]. Under stress, the endoplasmic reticulum activates inflammatory pathways that trigger insulin resistance, thereby leading to release of free fatty acids in plasma. An increase in circulating free fatty acids is associated with ectopic deposition of fat in the myocardium through downregulation of peroxisome proliferator-activated receptor- α in rodent models [17]. It is unclear if these findings can be extrapolated verbatim to human cardiomyocytes as well, but it does appear that there is a mismatch between the fatty acid supply and utilization in states of insulin resistance, which promotes steatosis in the myocardium. The problem is further accentuated by the decrease in maximal fatty acid oxidation capacity of the mitochondria in heart muscle, in the presence of an increased supply of fats [18].

Even though a healthy human heart predominantly uses fatty acids for ATP production during the normal physiological state, it can rapidly switch to glucose during times of stress [19]. The ability of the heart to switch between different substrates depending on the physiological and pathological stressors, substrate availability and oxygen supply is crucial for its optimal performance [19]. Decreased insulin sensitivity is associated with the decreased ability of the heart to switch to glucose use at times of stress, e.g. during ischemia, heart failure or pathological hypertrophy [20]. In this regard, Peterson et al. [21] demonstrated that obese females had higher myocardial oxygen consumption, and increasing BMI was a predictor of decreasing efficiency of myocardium in oxygen utilization. Decreased efficiency of heart in states of stress is a hallmark of early heart failure.

Recent work supports that mitochondria in the myocardium of people with diabetes might be a source of increased reactive oxygen species (ROS) [18]. These ROS can oxidize and damage intracellular lipids and proteins. ROS are also known to damage mitochondrial DNA and further impair mitochondrial respiration [19]. The changes in myocardial substrate utilization, ultrastructure, calcium handling, mitochondrial uncoupling, increased ROS production, lipotoxicity, local inflammation, and apoptosis have been implicated in

pathogenesis of diabetic or metabolic cardiomyopathy. The understanding of this entity is far from complete. More studies are required to unravel the complicated mechanistic details.

Obesity, Heart Failure and Stroke

Heart failure has been long established as risk predictor for future CVD events. In this context, previous work suggests that the risk of stroke among heart failure patients is almost seven times higher than in the general population [22, 23]. The link between obesity and heart failure is emerging; however, an often neglected consideration in the obesity epidemic is the preponderance of stroke. It is estimated that approximately 1 of every 15 deaths or approximately 700,000 people experience a new or recurrent stroke each year [23]. In this context, stroke is the third leading cause of death after heart disease and current thought lends to the perception that the increase in stroke events is driven by increasing incident and prevalent hypertension, diabetes, or atrial fibrillation [23–26]. However, when considering known predictors of stroke including diabetes mellitus, hypertension, dyslipidemia and tobacco use, the importance of obesity in driving the recent increases in incident stroke becomes evident.

Data from several recent meta-analyses would support this trend in obesity and risk for stroke [27, 28]. One recent meta-analysis including two million participants suggests that there is a graded positive relationship between obesity and incident ischemic stroke [27]. Another meta-analysis from a Japanese population demonstrates a very specific linear association between increases in BMI and ischemic and hemorrhagic stroke [28]. Interestingly, this study highlights a positive association between progressive increases in BMI within the normal and overweight range (20–29) and risk of CVD. An analysis of the Framingham study also pointed to the positive association between overweight (BMI 25–29.9) and relative risk of hypertension and cardiovascular sequelae [29]. Further analyses of Framingham data indicate that abdominal obesity after clinical adjustments for diabetes, hypertension and other CVD risk confounders, independently increases the risk for stroke, heart failure and all-cause mortality in men [30]. This would highlight obesity as a central driver of the heart failure-stroke risk.

Most concerning in understanding this relationship between obesity, heart failure and stroke are the increasing adolescence obesity rates. Data from this meta-analysis of 63 studies supports that obese children are at increased risk for type 2 diabetes, hypertension, dyslipidemia and future risk for heart failure and stroke [31]. These data would further suggest that if these children lost weight, future CVD risk would be attenuated. Cumulative data on obesity and cardiovascular risk would suggest weight loss in general would improve risk parameters such as diabetes, high blood pressure, and lipids, but long term work has yet to elucidate the beneficial impact of weight loss on hard cardiovascular endpoints

Obesity-Related Heart Failure as the Intermediate in the Cerebrorenal Connection

Congruent with an obesity epidemic, there is an exponential increase in chronic kidney disease (CKD) in the general population. Similar to the risk observed with increases in BMI and cardiovascular outcomes such as heart failure and stroke, there exists a graded relationship between increases in BMI and incident CKD and microalbuminuria [32, 33].

This is illustrated over numerous population-based studies estimating the relative risk for CKD in relation to increases in BMI [25]. This association holds true even after clinical adjustments for diabetes and hypertension [32, 33]. In this regard, BMI ≥ 30 in males and BMI ≥ 35 in females is associated with a 3- to 4-fold increased risk for CKD. The risk between obesity and CKD is augmented in the presence of other CKD risk factors such as diabetes and hypertension.

It is well accepted that there exists a graded relationship between reductions in estimated glomerular filtration rate or increases in proteinuria and CVD morbidity and mortality including heart failure and stroke [34, 35]. However, it is increasingly recognized this relationship is bidirectional in nature and is often referred to as the CRS [5]. When considering metabolic risk factors for both heart and kidney disease such as diabetes, hypertension, dyslipidemia or aging, we refer to this as the CRS. The physiology of the CRS involves a complex intersection of reductions in renal perfusion pressure, alterations in tubuloglomerular feedback and altered intrarenal hemodynamics from progressive heart failure. In turn, neurohormonal systems such as inappropriate activation of the sympathetic nervous system and renin-angiotensin-aldosterone system that arise from both heart failure and kidney disease integrate the impact that obesity has on CVD including stroke.

While we know much about the relationship between obesity, heart failure and kidney disease, there is increasing interest in how this relates to cerebrovascular disease. Recent work would suggest that the risk for stroke including transient ischemic attacks is inordinately high in the presence of CKD compared to other cardiovascular outcomes [36, 37]. However, findings from these studies appear to hold true only for those with CKD due to diabetes or hypertension. Data from The Atherosclerosis Risk in Communities (ARIC) study would suggest the risk for stroke is further modified by the presence of anemia [37] whereas data from a Japanese cohort suggests this relationship exists independent of other effect modifiers like diabetes, hypertension or anemia [38]. In essence, these collective findings suggest that perhaps CKD accelerates atherosclerosis in the presence of other cardiovascular risk factors, yet it is unclear whether the presence CKD alone may be insufficient as an independent risk factor for stroke.

Conclusions

In summary, there is an emerging interest in the effect that obesity has on heart failure as a mediator of cardiovascular outcomes including stroke and kidney disease. Overnutrition with our Western diet contributes substantially to a prooxidative/inflammatory milieu that promotes alterations in fatty acid, lipid and glucose metabolism that influence myocardial function and the progression of heart failure from diastolic to systolic failure. In this regard, progressive heart failure is well documented to be associated with CKD referred to as the CRS, and is a significant prognosticator for cerebrovascular disease (e.g. stroke). Whether this relationship between obesity, heart disease/failure and risk for CKD and stroke is direct or a confluence of risk factors is unknown.

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Fig. 1.

Obesity is a proinflammatory state that has detrimental effects on multiple organ systems independent of the known risk factors for CVD. The role of obesity in causing cerebrovascular disease and CKD, independently or via pathogenesis of heart failure, is depicted here.