



Role of Obesity in the Pathobiology and Treatment of Heart Failure with Preserved Ejection Fraction in Diabetes Mellitus

Abhishek Jaiswal*

Hartford HealthCare Heart and Vascular Institute, Hartford Hospital, Hartford, USA

Abstract

Overlapping epidemics of obesity, type 2 Diabetes Mellitus (DM) and heart failure goes beyond just coexistence. As obesity-related heart failure with preserved ejection fraction (HFpEF) is increasingly recognized as a distinct phenotype, it remains unclear whether obesity is a key contributor, an epiphenomenon or merely a frequent comorbidity in patients with DM and HFpEF. Although DM is an independent risk factor for heart failure in the absence of obesity, coronary artery disease and hypertension, myocardial alterations or diabetic cardiomyopathy rarely progress to the clinical syndrome of heart failure. On the other hand, obesity is the most common modifiable risk factor for HFpEF, more than twice as common as DM; and, obesity-associated insulin resistance, endothelial dysfunction, inflammation, and oxidative stress results in DM and HFpEF. The positive cardiovascular outcome of antidiabetic drugs seems to be mediated by the positive impact on adiposity independent of glycemic control- implying that obesity is a key contributor to the development of HFpEF in DM. It is likely that HFpEF in DM is a phenotype of obesity-associated HFpEF. This paradigm has a major consequential effect on the management of patients with DM and HFpEF. As new-onset HF or worsening of pre-existing HF is increasingly recognized as a relevant clinical outcome in DM and vice-versa; it is imperative that clinical studies of new agents for DM and HF need to address their impact on obesity.

Keywords

Obesity; Heart Failure with Preserved Ejection Fraction; Diabetes Mellitus; Heart Failure; Vascular Stiffness

Introduction

In the absence of coronary artery disease (CAD), both heart failure due to reduced ejection fraction (HFrEF) or associated with preserved (HFpEF) in type 2 diabetes mellitus (DM) is attributed to diabetes cardiomyopathy that is characterized by DM-related myocardial alterations [1,2]. Chronic hyperglycemia, insulin resistance and traditional risk factors, including hypertension, obesity, and dyslipidemia have been proposed to contribute to the pathobiology of HF in DM. On the contrary, however, most anti-hyperglycemic drugs do not affect HF clinical outcomes [3]. Moreover, insulin resistance is rare in the absence of central adiposity; and, obesity independent of insulin resistance contributes to the development of DM, hypertension, and dyslipidemia [4]. But even more notably metabolically healthy obese are at increased risk of HF [5]. Indeed, the patients with DM who develop HFpEF are overweight or obese. Obesity triggers and nurtures insulin resistance, inflammation, oxidative stress, and endothelial dysfunction, promoting cardiovascular remodeling and DM (Figure 1). Not surprisingly, obesity is the most common modifiable risk factor for the development of HFpEF [6]. Further, the anti-glycemic agents which have a positive impact on HF achieve only modest glycemic control but mediate weight loss and facilitate urinary sodium excretion. For the above reasons, it appears that obesity is likely an independent contributor to the development of HFpEF in DM. The present review explores the essential role of obesity in the pathogenesis of HFpEF in DM and discusses the importance of obesity management in the successful treatment of HFpEF in DM. Inclusion of obesity as an endpoint in addition to HF in the clinical trials of anti-hyperglycemic agents might further help delineate the role obesity plays in the pathogenesis of HFpEF in DM. Similarly, clinical trials in HFpEF need to address the effect of any intervention on obesity and DM.

DM and HFpEF

Rubler et al. proposed diabetic cardiomyopathy in four patients with T2DM and glomerulosclerosis who at autopsy had cardiomegaly and myocardial changes in the absence of CAD and HTN [1]. Subsequently, Framingham and Strong Heart Studies found an increased risk of HF in patients with DM independently of age and comorbidities [7,8]. A 4 fold higher prevalence of HF has been reported in diabetic than non-diabetic patients: 12.0

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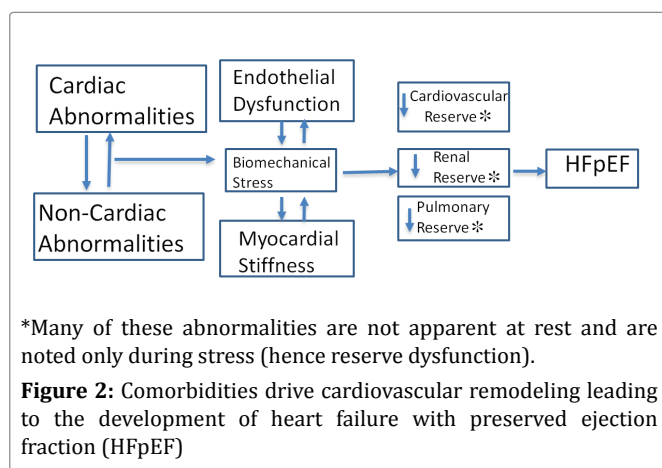
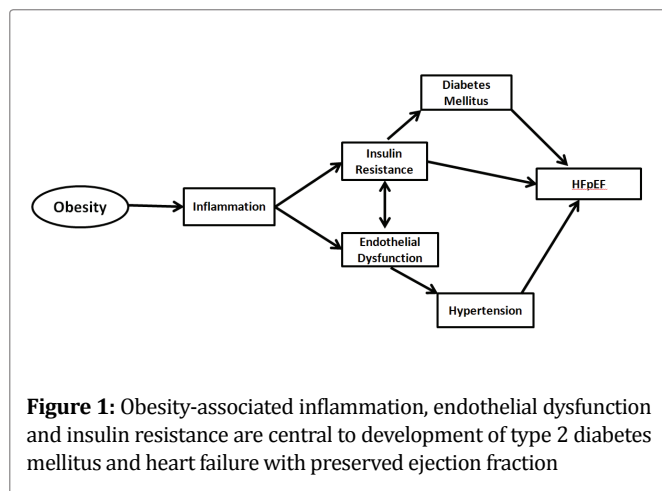
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*Corresponding author:

Abhishek Jaiswal
Hartford Health Care Heart and Vascular
Institute
Hartford Hospital
Hartford, USA
Tel: 1-860-972-1212
Fax: 1-860-545-3269
E-mail: Abhishek.jaiswal@hhhealth.org

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vs.3.0% [9]. The presence of HF in DM portends poor outcomes [10]. Similarly, DM is common and associated with a poor clinical outcome in HFpEF [10-12]. The burden of HFpEF in diabetic patients has been specifically assessed in the DIABHYCAR (Diabetes, Hypertension, Cardiovascular Events, and Ramipril) study where half of newly diagnosed HF patients had HFpEF [13]. Further, over a follow up of 4 years, a community-based study of 6814 individuals without CAD uncovered that increasing index of metabolic syndrome correlated with increasing HF risk, with two-thirds of these patients developing HFpEF [14]. The risk of DM-related poor clinical outcomes appears compared with HFrEF and HFpEF [15]. However, while DM is an independent risk factor for developing HF, the risk is modest. In a prospective study of 2717 elderly (mean age 81 years), the risk of developing HF was greater with HTN or CAD than with DM (a 4.0, 2.5 and 1.3 times, respectively) [16]. Young patients with DM who develop HFpEF are likely obese with HTN or renal impairment compared with HFpEF patients without DM [17]. Health maintenance data revealed that the presence of HTN, renal impairment, and ischemic heart disease increased the risk of HF in >8,400 patients with DM and without HF at entry [18]. Moreover, young patients with DM without neuropathy, nephropathy, obesity, hypertension or CAD rarely has HF; and, the progression of subclinical diabetic cardiomyopathy might be very slow, spanning over a period of even two decades in DM [19]. Taken together, in the absence of CAD and advanced age, obesity and comorbidities might play a major role in the development and progression of HFpEF in DM.

Obesity

Obesity is associated with HFpEF independent of ischemic injury; and, conversely, weight loss improves LV mass, diastolic dysfunction (DD) and HF severity [20,21]. The pathobiology associated with obesity seems to be mediated through an imbalance in leptin-

aldosterone-neprilysin axis, and obesity-associated inflammation [22]. Through its action on the hypothalamus, leptin plays an important role in energy demand and supply by promoting satiety. In a normal individual transient release of leptin promotes vasodilation, natriuresis and decreased myocardial contractility. A persistently elevated level of leptin and selective leptin resistance in obese patients promotes sympathetic and renin-angiotensin-aldosterone systems activation enhances sodium retention and causes cardiovascular remodeling and HTN [23] (Figure 2). Elevated leptin levels, however, do not fully account for the obesity-associated risk of HF [24]. Beyond leptin, other pro-inflammatory adipokines promote mitochondrial lipid oxidation, structural and functional myocardial derangements [25]. Increased circulating inflammatory cytokines released from macrophages and adipocytes in adipose tissues impair insulin signaling and glucose metabolism resulting in insulin resistance. Obesity-associated pro-inflammatory state inhibits the secretion of adiponectin-an adipokine that minimizes the risk of HF and contributes to hyperleptinemia by promoting leptin release from adipocytes [26,27]. In addition, obesity or a high-fat diet may induce resistance to adiponectin actions [28]. This increase in leptin and a deficiency, as well as resistance in adiponectin, contribute to obesity-related-HFpEF. Importantly, volume overload suppresses adiponectin release and thus, in turn, mediates steady HFpEF deterioration [29]. In addition to the imbalance in adipokine levels, neprilysin, which is responsible for the degradation of endogenous natriuretic peptides, is increased in obese patients. Natriuretic peptides have important adaptive cardiovascular effects, including natriuresis, suppression of aldosterone from the adrenal gland, and which inhibits cardiac inflammation and fibrosis. Besides increased neprilysin release by adipocytes elevated renal sympathetic nerve activity contributes to enhanced activation of neprilysin in obese. In turn, neprilysin promotes adipogenesis by inhibiting natriuretic peptide stimulated lipolysis and adipocyte differentiation. Overactivity of neprilysin may increase leptin release by adipocytes which in turn promote neprilysin secretion by augmenting renal sympathetic nerve activity resulting in a positive feedback loop [22,23].

Heterogeneity of Obesity

A body mass index (BMI) of $\geq 30\text{kg/m}^2$ has traditionally been used to diagnose obesity. However, cardiometabolic perturbations are more dependent on the distribution of fat depots and fat composition than overall obesity as reflected by BMI [30-35]. Obesity as measured by BMI underestimates the contribution of adiposity to cardiovascular diseases. Visceral adipose tissue (VAT) may accumulate in individuals with normal BMI [32]. As BMI does not differentiate lean mass from fat mass, this surrogate may have limitations in individuals with excess body fat and normal range BMI. Since only 5-15% of total fat resides in the visceral compartment, the total amount of VAT may not be estimated from body weight or BMI [33]. Conversely, up to a third of patients with elevated BMI do not accumulate visceral fat, and have minimal metabolic alterations [34]. Visceral fat is pivotal in the development of obesity-associated pathobiology independently of total body fat mass. Indeed, a specific type of obesity defined as 'metabolically obese normal weight' is now recognized. This normal weight and BMI individuals present with hyperinsulinemia, insulin resistance and DM [35]. Importantly, several observations have linked visceral obesity with HF independently of BMI [32-35]. Adipose tissues can accumulate into intraperitoneal, mesenteric, retroperitoneal, epiploic, gonadal and pericardial/epicardial adipose tissue. Interestingly, the amount of Epicardial adipose tissue (EAT) correlates with that of VAT and EAT might play an essential role in cardiac function and homeostasis. The amount of EAT correlates with increased cardio-metabolic risk, LV mass, systolic and diastolic dysfunction independent of BMI [36].

While in non-obese EAT protects and nurtures the heart; in obese with chronic energy balance, under excessive fat accumulation, it promotes inflammation, microvascular dysfunction, and cardiovascular steatosis and hence bolsters cardiovascular risk [37]. In addition to increased EAT, obese patients with T2DM also

have dysfunctional EAT [37]. In addition, EAT increases leptin concentration [38] which seems to promote the pathobiology of HFpEF. Moreover, the regression of EAT correlates more closely with improvements in LV mass and function than BMI and waist circumference [39,40]. Beyond the distribution of fat depots, variability in a fat composition is important for the development of metabolic abnormalities. In a normal adult, white adipose tissue (WAT) predominates and primarily acts as a storage site for excess calories for use in times of scarcity or need. A small amount of brown adipose tissue (BAT) is found dispersed in various WAT depots in adults and generates non-shivering thermogenesis and energy dissipation by oxidation of glucose and fatty acids, and deviation of electron transfer from ATP synthesis to heat generation. When confronted with chronic caloric excess, uptake of excess free fatty acid results in hypertrophy of WAT in VAT where it stimulates the production of pro-inflammatory adipokines, oxidative stress and activates renin-angiotensin-aldosterone system (RAAS). The propensity to accumulate preferentially WAT in VAT under conditions of excess energy intake is regulated by age, gender, growth hormones, nutritional factors, physical activity, and the endocannabinoid and hypothalamus-pituitary-adrenal systems [41]. Excess fat is deposited around the myocardium once VAT storage is saturated leading to an increase of EAT thickness and subsequent myocardial steatosis and dysfunction. BAT, on the other hand, becomes reduced, atrophied and inactive, losing its protective anti-hyperglycemic, dyslipidemic and anti-inflammatory effects. Reduced activity of BAT may predispose subjects to T2DM not only by increasing obesity but also by reduction of glucose uptake [42].

Hyperglycemia is commonly implicated as an important risk factor for HF in DM; the incidence of HF increases as the level of glycated hemoglobin rises [43]. However, compared to patients with type 2 DM, type 1 DM patients are less likely to experience HF despite poor glycemic control [44]. Moreover, the pre-diabetic state is associated with an increased HF risk despite the only modest elevation of blood glucose levels. Thus it seems that type 2 DM-related hyperglycemia may not play a preponderant role in the pathobiology of HF in DM. Both type 2 DM and prediabetic states are associated with insulin resistance and thus it is likely hyperinsulinemia rather than hyperglycemia might be an important driver of HF [4]. On the other hand, Insulin resistance and associated hyperinsulinemia may be present for decades before patients develop HF [45]. Obesity is likely needed to accelerate the development of HF through both the promotion of insulin resistance and the activation of other pathways [46]. Importantly, endothelial dysfunction contributes to and exacerbates insulin resistance by limiting glucose delivery to target tissues [47]. The relationship between obesity and insulin resistance is bidirectional: insulin resistance causes AT inflammation and AT inflammation mediates insulin resistance. Insulin resistance promotes inflammation in VAT mediated through monocyte chemoattractant protein-1 [32]. Indeed, after the reversal of obesity, no association between insulin resistance and LV mass could be found in the Framingham study subjects [48]. Further, weight loss reverses insulin resistance in DM [49]. Similar mechanisms mediate LV dysfunction in obese and in patients with DM; metabolic disturbances, oxidative stress, activation of RAAS system and myocardial remodeling [50].

Furthermore, obesity promotes vascular stiffness through RAAS activation that is mediated by oxidative stress and endothelial dysfunction [51-55]. On the other hand, hyperactive RAAS promotes obesity by helping adipocyte differentiation, insulin sensitivity of adipocytes and body fat accumulation providing a positive feedback loop [51]. Endothelial dysfunction promotes arterial stiffening through proliferation, hypertrophy, remodeling, and apoptosis of smooth muscle cells and, in turn, arterial stiffening reduces vascular compliance that is paramount in the development of HTN and myocardial alterations and hence HFpEF [51,56,57]. In a stiff arterial system, incident pulse wave resulting from stroke volume travels faster resulting in an early arrival of the reflected wave in systole and enhancement of the central systolic BP and LV afterload. Further, the rapid return of the reflected wave toward the heart

decreases central diastolic pressure and hence coronary perfusion pressure [56]. Arterial stiffening also increases pulsatile shear, exacerbating endothelial dysfunction and vascular disease [57]. Not surprisingly, weight loss improves arterial compliance [53,54]. The proposed paradigm where obesity is central to HFpEF development has important diagnostic and therapeutic implications that may drive clinical outcomes.

Therapeutic Implications

Control of hyperglycemia is perceived as essential in the prevention of new-onset or worsening of pre-existing HF—an important cause of mortality in patients with DM. Although poor glycemic control in DM increases HF, intensive glycemic control may not improve/reverse clinical HF [58-60]. It is possible that in patients with long-standing DM and established HF glycemic control is not beneficial; and, an early glycemic control might provide protection against the development of HF over the long term. However, the longest follow up (27 years) of a large cohort of young patients with type 1 DM (mean age 49 years) failed to show any association between glycemic control and cardiac size, geometry, and function [61]. The pathobiology, of HFpEF, may be more closely linked to hyperinsulinemia and oxidative stress than to hyperglycemia. Increased insulin signaling along with inflammation promotes obesity and water and salt retention [62]. From a therapeutic perspective, although weight loss-induced lowering in HbA1C reduces myocardial triglyceride content and insulin resistance and improves cardiac function; reduction of HbA1C with anti-hyperglycemic agents may worsen HFpEF [58-60,63]. Metformin and sodium-glucose co-transporter 2 (SGLT-2) inhibitors are the anti-hyperglycemic agents that might benefit HFpEF in patients with DM [64,65]. The modest glycemic control achieved by these agents contrasts with their cardiovascular benefit—implying non-hyperglycemic pathobiology in the development of HF. It appears that the differential actions of antidiabetic drugs on body weight, VAT and associated pathobiology underlie these divergent results. The effects of Metformin and SGLT-2 inhibitors on obesity and inflammation are likely to underline their beneficial cardiovascular effects. Loss of body weight and particularly of VAT and improved vascular function may reduce HFpEF incidence in diabetic patients receiving metformin and SGLT-2 inhibitors [66,67]. Although obesity is detrimental in HFpEF weight loss medications are not all beneficial: SGLT-2 inhibitors reduce EAT inflammation and dysfunction; while dipeptidyl peptidase-4 inhibitors increase EAT and inflammation [67,68]. Furthermore, GLP-1 agonist-induced weight loss does not improve obesity-related AT dysfunction [69]. Hence, metformin and SGLT2 inhibitors reduce the risk of HF events in patients with DM, who are prone to develop obesity-related HFpEF.

Thus far, no prospective randomized study has evaluated the role of metformin in patients with DM and HF. Review of cohort and administrative databases suggest metformin alone or in combination decreased mortality in patients with DM and HF [70]. In UKPDS, metformin reduced all diabetes-related endpoints including HF independent of glycemic control. Most of the benefits of metformin were seen in obese with DM [71]. Metformin induces weight loss, significantly reduces the progression of insulin resistance to DM by 30% after 3 years and up to 25% after 10 years of treatment [72]. Metformin also improves endothelial function and reduces inflammation [73]. Similarly, Improvement in vascular stiffness and BP in conjunction with the reduction in plasma volume and sodium might explain the reduction in HF hospitalization and cardiovascular mortality after treatment with SGLT-2i [74]. Beyond the role of anti-hyperglycemic agents, primary management of obesity provides additional benefits in the prevention and worsening of HFpEF in DM. An intensive lifestyle is associated with a reduction in HF events that decrease VAT, inflammation and insulin resistance [75]. In addition, surgical weight loss can normalize glucose tolerance in patients with DM and obesity [76]. Ongoing studies are evaluating the effects of empagliflozin in patients with HFpEF, with and without diabetes. The lack of benefit from sacubitril/valsartan in the PARAGON-HF trial despite higher neprilysin levels in obese patients resulting in a

relative deficiency of natriuretic peptides is disappointing. However, the implication of this result might be limited due to exclusion of morbidly obese patients from the study. Further, aldosterone has been implicated in obesity, insulin resistance and DM related vascular complications [22,23]. Therefore, mineralocorticoid antagonists might have value in the management of DM and HF beyond contemporary practice. Reduction in BP is associated with better cardiovascular outcomes in patients with DM than in patients without DM [77]. Even a small systolic BP difference of 5 mm Hg and a diastolic BP difference of 2mm Hg were associated with a 14% reduction in all-cause mortality and 18% risk reduction in cardiovascular mortality. Moreover, antihypertensive drugs may have a differential effect on obesity and DM; hence the clinical outcome. Altogether, one needs to examine the effect of anti-hyperglycemic drugs on VAT as obesity appears central to the development and worsening of HF in DM. In clinical practice, an obesity/endocrine-HF clinic is an attractive approach given the common coexistence, differential effects of anti-hyperglycemic agents on HF and shared risk factors.

Summary

In Aggregate, it is likely that obesity independently contributes to and accelerates the progression of HFpEF in T2DM. The effects of anti-hyperglycemic medications on HFpEF and obesity need to be systematically investigated. Management of obesity might be an effective strategy for reducing cardiovascular complications in DM.

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