

New-Onset Diabetes in Heart Failure Patients: A Complex Relationship with Clinical Implications

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ABSTRACT

The relationship between heart failure and diabetes mellitus (DM) is bidirectional. DM is a known risk factor for the development of heart failure and is related to a worse outcome. On the other hand, some studies have found that heart failure is also associated with a greater incidence of new-onset diabetes. This relationship has been less evaluated and the underlying mechanisms are not fully understood. We present the evidence linking heart failure with insulin resistance and the development of DM, as well as the possible mechanisms. Furthermore, medications that have been shown to improve clinical outcomes in patients with chronic heart failure may be associated with the development of incident diabetes whereas some hypoglycemic agents raise safety concerns in these patients. Therefore, we will consider pharmacologic interventions that can reverse insulin resistance in this specific population.

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Key words: Beta-blockers; Heart failure; Insulin resistance; Insulin sensitizers; Renin-angiotensin-aldosterone system; Type 2 diabetes

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INTRODUCTION

Heart failure and diabetes mellitus (DM) are chronic diseases that frequently occur in the same patient^[1,2]. They have a bidirectional relationship since each condition may impact on the other in terms of causation and outcome (Figure 1). In this regard, DM, characterized by insulin resistance and β -cell dysfunction, is a recognized risk factor for the development of heart failure and this risk increases proportionally as metabolic control worsens^[1,3,4]. Heart failure is up to five times more frequent in patients with DM^[5,6] and has increased morbidity and mortality^[7-10]. Data from the Uppsala study showed that insulin resistance precedes and predicts the development of chronic heart failure, independently of established risk factors for heart failure including diabetes itself^[11]. More recently, Vardeny *et al*^[12] provided further support for the incremental risk of heart failure in nondiabetic participants with insulin resistance in the Atherosclerosis Risk in Communities (ARIC) study.

On the other hand, predictors of diabetes in the general population are well established and include anthropometric adiposity parameters, dysglycemia markers and risk scores^[13]. However,

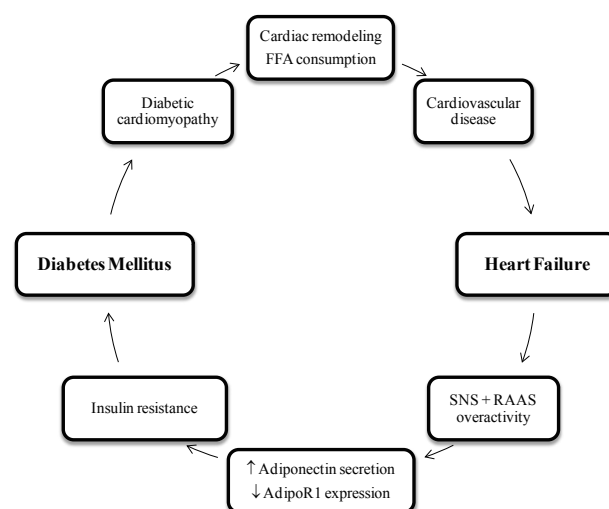


Figure 1 Bidirectional relationship between diabetes mellitus and heart failure. AdipoR1, adiponectin receptor 1; FFA, free fatty acids; RAAS, renin-angiotensin II-aldosterone system; SNS, sympathetic nervous system.

some studies have stressed the fact that patients with heart failure also have an increased risk of developing DM^[14-20]. This causal relationship has been less evaluated and the mechanisms underlying this association are not clearly understood. Interestingly, there has been a shift in the understanding of heart failure in the last decade. In this respect, beyond traditional hemodynamic factors and neurohormonal activation, it is increasingly suggested that chronic heart failure is a much more complex systemic disease involving metabolic derangements that implicate organs such as adipose tissue and skeletal muscle, and the endocrine system, through leptin, adiponectin and insulin-like growth factor. Thus, we considered of interest to review the available evidence linking heart failure with insulin resistance and the development of DM.

EPIDEMIOLOGIC EVIDENCE LINKING HEART FAILURE WITH NEW-ONSET DM

Nearly 25% of all patients participating in major heart failure clinical trials were diagnosed with diabetes at entry compared with only 7% of the general population^[21,22]. In the Randomized Evaluation of Strategies for Left Ventricular Dysfunction (RESOLVD) pilot study^[15], 43% of patients had either clinically-overt diabetes or preclinical abnormalities of glucose metabolism at the time of enrollment. On the other hand, different studies have reported an increased incidence of DM in patients with heart failure who were normoglycemic at baseline. The first demonstration of the high risk of developing diabetes was by Amato *et al*^[14] in a longitudinal study of elderly patients with heart failure. DM during the 3-year follow-up occurred in 28.8% of patients with heart failure and 18.3% of controls. Heart failure was a risk factor for developing DM regardless of age, sex, body mass index or drug therapy with a 1.4 age-adjusted relative risk. In the Bezafibrate Infarction Prevention (BIP) study^[16], the mean baseline glucose concentration was shown to increase during 7.7 years of follow-up in 2,616 non-diabetic patients. DM developed in these patients in a stepwise manner, from 13% in those with a New York Heart Association (NYHA) class I to 20% in patients with NYHA functional class III. A subanalysis of the Studies Of Left Ventricular Dysfunction (SOLVD)^[17] found a DM incidence of 5.9% during a mean follow-up of 3 years in the enalapril-treated arm and 22.4% in the placebo group. These results concur with those reported by the Carvedilol or Metoprolol European Trial (COMET)^[19], in which DM was diagnosed during follow-up in 10.3% and 12.6% of patients receiving carvedilol or metoprolol, respectively. A recent study evaluating incident diabetes in patients with cardiovascular disease, heart failure, renal disease or depression found heart failure to be the major independent predictor of incident DM, with a 48% increased risk compared with those without heart failure^[20]. In non-diabetic patients with chronic heart failure in the Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM) program^[23], AIC and body mass index were the main factors associated with new-onset diabetes.

Thus, according to the above-mentioned studies, the risk of incident DM in subjects with heart failure is 10 to 48% higher than in the general population adjusted for age.

HEART FAILURE AND INSULIN RESISTANCE

Although epidemiologic studies have established the association between heart failure and the development of DM, the underlying pathophysiologic explanation remains to be clarified. Several lines of clinical research suggest that heart failure is an insulin-resistant state responsible for the increased incidence of DM in these

patients. Clinical studies in the early 1990s using the euglycemic hyperinsulinemic clamp demonstrated the existence of fasting hyperglycemia and insulin resistance in patients with heart failure, regardless of the etiology^[24,25]. Similarly, in 38 patients with heart failure and ventricular systolic dysfunction, 58% decreased insulin sensitivity and a 131% increase in fasting insulin were found compared with healthy controls, regardless of the etiology of heart failure^[26]. In 129 patients with heart failure, Al Zadjali *et al*^[27] observed a 61% prevalence of insulin resistance, a condition that was associated with waist circumference, and triglyceride, high-density lipoprotein (HDL) cholesterol and leptin concentrations. Other studies also revealed a high prevalence of abnormal glucose metabolism in patients with heart failure. A study evaluating carbohydrate metabolism disorders in 94 heart failure patients found a 29% prevalence of known DM, a 15% prevalence of unknown DM, 24% presented oral glucose intolerance and 27% had insulin resistance (as defined by a homeostasis model assessment-insulin resistance above 2); thus, overall 94.6% of heart failure patients presented carbohydrate metabolism disturbances at the time of inclusion in the study^[28].

Additionally, several studies reported a direct relationship between the severity of heart failure and insulin resistance, with decreased functional exercise capacity or increased B-type natriuretic peptide levels being associated with greater insulin resistance^[25,27]. Swan *et al*^[26] demonstrated that increased heart failure severity, in terms of reduced exercise capacity, correlated with increased insulin resistance, regardless of the etiology of heart failure. These results concur with those of other studies in which insulin resistance increased progressively with worsening of heart failure functional NYHA class^[15,19,29]. Berry *et al*^[30], in 454 consecutive patients admitted with acute heart failure, confirmed that abnormal glucose tolerance was a strong predictor of in-hospital mortality.

Taken together, these data indicate that the prevalence of insulin resistance in patients with heart failure is high and correlates with its severity. Furthermore, the prognostic value of insulin resistance is independent of other parameters including left ventricular ejection fraction and peak oxygen consumption, which may imply that insulin resistance could have a pathogenetic role rather than just be a severity marker.

MECHANISM OF INSULIN RESISTANCE IN PATIENTS WITH CHRONIC HEART FAILURE

Heart failure is a complex clinical syndrome that results from any structural or functional impairment of ventricular filling or ejection of blood associated with local and systemic metabolic derangements and the development of a progressive catabolic state^[31]. Pathologic changes associated with insulin resistance and compensatory hyperinsulinemia are shown in figure 2. The exact mechanisms by which heart failure is accompanied by resistance to the metabolic actions of insulin are unknown, although several possible pathogenetic mechanisms have been involved.

Overactivity of the sympathetic nervous system

This is the most accepted pathway. Elevated norepinephrine levels correlate with the hemodynamic parameters of heart failure, as with insulin sensitivity and glucose tolerance^[24,32,33]. Since the peripheral uptake of glucose and insulin in skeletal muscle is mediated by the vascular tone of afferent arterioles, arteriolar vasoconstriction triggered by the stimulation of α -adrenergic receptors causes blood flow to bypass skeletal muscle with a subsequent decrease in glucose utilization^[34].

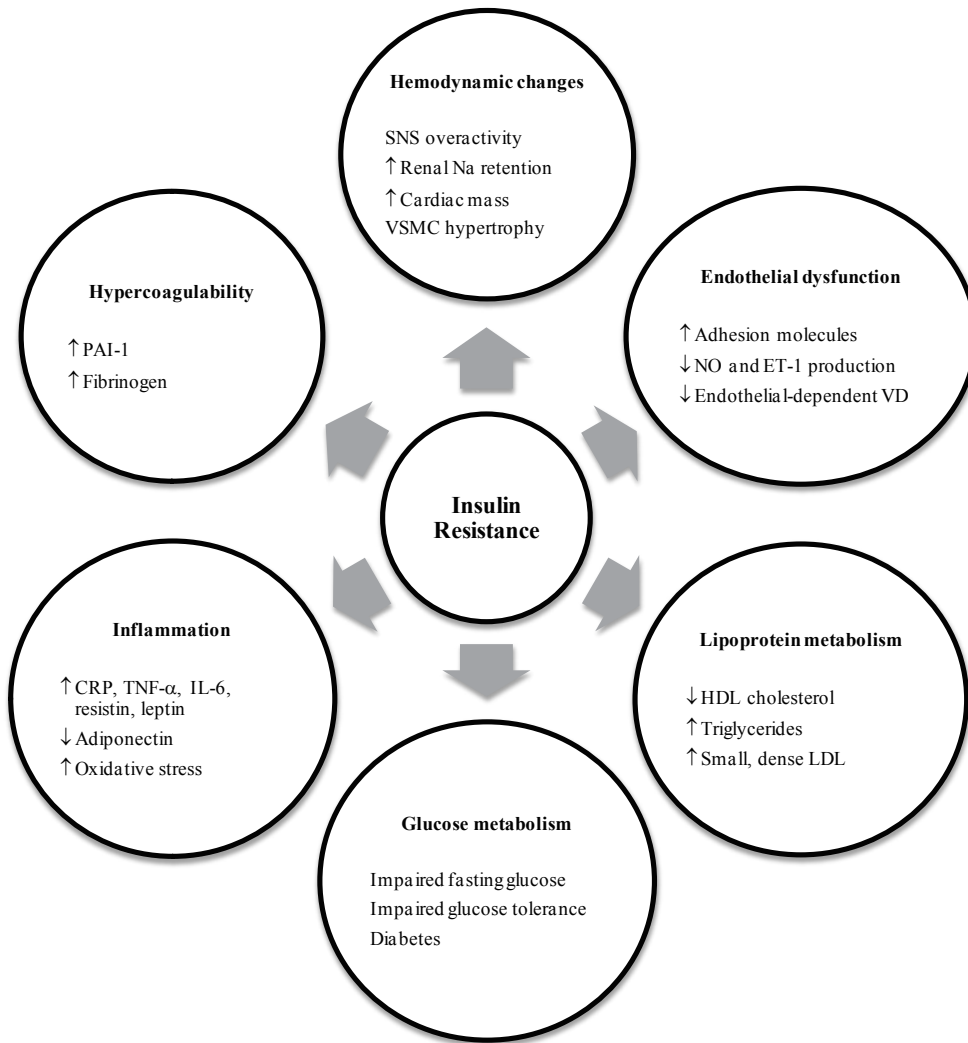


Figure 2 Cardiometabolic impact of insulin resistance. CRP: C-reactive protein; ET: endothelin; HDL: high-density lipoproteins; IL: interleukin; LDL: low-density lipoproteins; Na: sodium; NO: nitric oxide; PAI: plasminogen activator inhibitor; TNF: tumor necrosis factor; VD: vasodilatation; VSMC, vascular smooth muscle cells.

Moreover, the activity of the sympathetic nervous system increases lipolysis in adipose tissue through direct activation of the β -adrenergic cell receptor, thereby increasing circulating free fatty acid concentrations^[35]. In patients with heart failure, higher baseline norepinephrine levels correlate with those of free fatty acids, and the decrease in the free fatty acids mediated by insulin is dimmed compared to individuals without heart failure^[24]. The increase in free fatty acids inhibits glucose uptake mediated by insulin in skeletal muscle. In addition, free fatty acids raise endogenous glucose production by activating hepatic glycogenolysis^[36].

Sympathetic nervous system overactivity, as indicated by elevated heart rate, has also been associated with decreased insulin sensitivity and compensatory hyperinsulinemia in populations without heart failure^[37,38]. Although sympathetic hyperactivation as a cause of insulin resistance in heart failure has been the most promulgated theory, some studies found no correlation between plasma levels of norepinephrine and insulin resistance^[26,27], suggesting that other factors may influence the decline in insulin sensitivity in heart failure patients.

Adiponectin resistance

Adiponectin is a key adipokine which, together with leptin and resistin, contributes to the regulation of energy homeostasis by

improving insulin sensitivity. It exerts multiple further actions, such as increasing endothelial function, and has antiapoptotic, anti-inflammatory and antiatherogenic effects (Figure 3). Circulating adiponectin in human plasma may form oligomers and multimers or may exist in monomers. Although the exact role of these isoforms is unclear, it seems that high-molecular-weight adiponectin is of particular importance as it binds to the adiponectin receptor 1 (AdipoR1) that is mainly expressed in skeletal muscle and to the AdipoR2 expressed in the liver to exert insulin-sensitizing and vasoprotective effects^[39]. While the adipocyte is well established as the predominant cell type to produce adiponectin, emerging data suggest cardiomyocytes^[40-42], skeletal muscle cells^[43,44] and other tissues as alternative adiponectin sources^[45]. However, it is unclear how much of this non-adipose expression contributes to the circulating adiponectin levels. Van Berendoncks *et al.*^[46] found a 5-fold increase in adiponectin expression in skeletal muscle cells of patients with mild to moderate chronic heart failure. In turn, a decreased receptor expression of AdipoR1 and target genes in lipid and glucose metabolism was observed. Thus, increased levels of circulating adiponectin in chronic heart failure could reflect a functional adiponectin resistance. Recent studies using a ventricular assist device suggested that this metabolic scenario could be reversible in patients with advanced heart failure^[47,48].

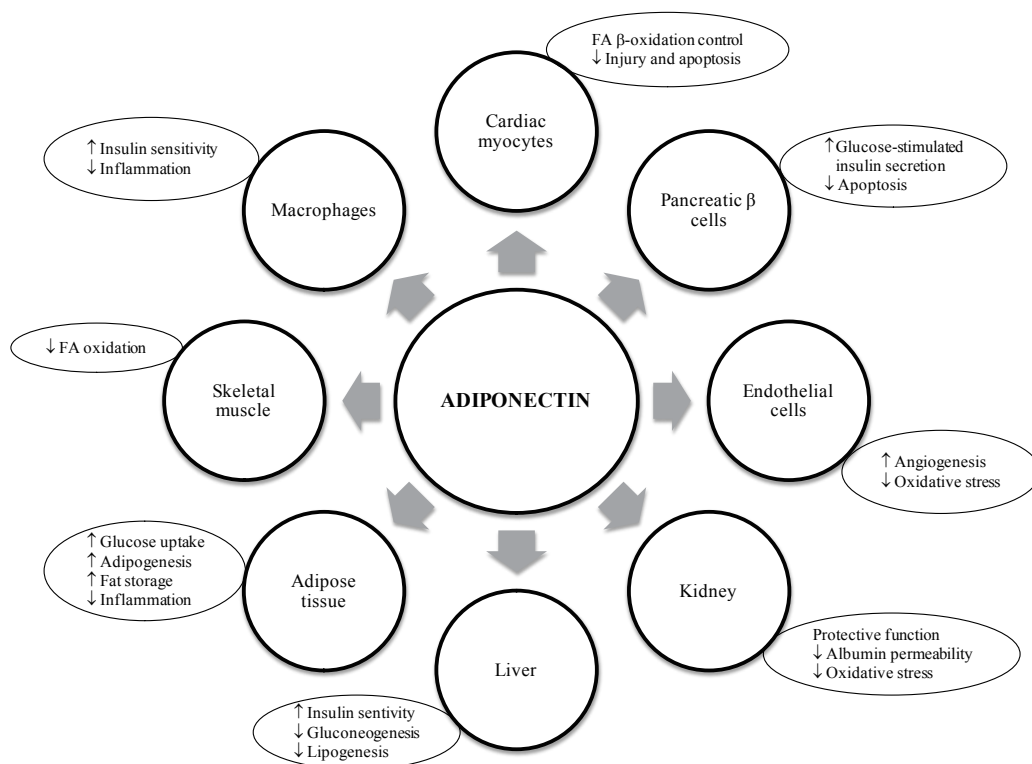


Figure 3 Endocrine effects and other adiponectin properties. FA, fatty acid.

Genetic predisposition

Patients who develop DM may have a genetic susceptibility to failure of the β-cell pancreatic secretory response to chronic hyperglycemia caused by insulin resistance. Thus, heart failure could select predisposed patients to develop DM by a reduction in the insulin sensitivity mediated by chronic activation of the sympathetic nervous system.

The clinical expression of DM usually requires the combination of resistance to peripheral actions of insulin and decreased insulin secretion in response to hyperglycemia^[49]. Resistance to insulin action results in decreased glucose uptake in skeletal muscle, decreased inhibition of hepatic glucose production and increased lipolysis and free fatty acid release from adipose tissue. Patients with heart failure may have decreased sensitivity to insulin and glucose intolerance without changes in basal glucose. Over time, however, the metabolic consequences of insulin resistance such as hyperglycemia and increased free fatty acids, in a genetically susceptible population, can result in reduced pancreatic β cell function. This exhaustion of β cells is associated with a decrease in the mass of pancreatic β cells mediated by apoptosis, as demonstrated in autopsy studies of DM patients^[50].

INSULIN RESISTANCE AND MYOCARDIUM

Glucose is a specially important substrate for the heart and influences both normal cardiac function and the response to ischemia that promotes glucose uptake and decreases the utilization of free fatty acids by the human heart. On the other hand, patients with chronic heart failure due to coronary artery disease are more likely to have abnormalities in glucose metabolism than patients with heart failure due to idiopathic dilated cardiomyopathy^[26].

The development of cardiac insulin resistance may occur independently of systemic insulin resistance; however, systemic insulin resistance significantly contributes to cardiac insulin

resistance owing to increased circulating levels of nutrients, oxidative stress and disturbances in the neurohumoral and cytokine balance^[51].

Insulin resistance is involved in potentially harmful metabolic dysfunctions that can affect energy supply and blood flow to the myocardium and skeletal muscle^[52,53]. Insulin increases glucose utilization and reduces myocardial free fatty acid oxidation by various mechanisms. Obtaining oxygen for glucose oxidation is more efficient than for fatty acid oxidation, and this modification in cardiac metabolism is theoretically beneficial to the heart, mainly during ischemia. This mechanism may have been responsible for the beneficial effects of glucose-insulin and potassium infusions observed in several clinical trials^[54,55].

The presence of insulin resistance or DM has been shown to affect glucose metabolism at different levels in the myocardium, from glucose uptake to final oxidation by mitochondria^[56-58]. These changes are responsible for reduced resting cardiac efficiency that may predispose to the development of diabetic cardiomyopathy, but also to increased susceptibility to ischemia. It is known that subjects with insulin resistance are at increased risk of heart failure and death compared with insulin-sensitive subjects and that these differences cannot be justified only by other risk factors such as hypertension or vascular disease^[59].

PHARMACOLOGIC INTERVENTION FOR INSULIN RESISTANCE IN HEART FAILURE

The clinical significance of insulin resistance in patients with chronic heart failure lies in potentially reversible metabolic changes, especially at early stages of cardiac dysfunction. Thus, since heart failure is an insulin-resistant state, insulin resistance may be considered a therapeutic target in these patients.

Lifestyle interventions are essential tools in the management of insulin resistance. Physical activity was shown to improve insulin

resistance in patients with impaired glucose tolerance in the Diabetes Prevention Project (DPP) study^[60]. Exercise training has proved to enhance muscle glucose uptake and reduce insulin resistance in patients with idiopathic cardiomyopathies^[61]. Diet and drug-induced weight loss studies have also been reported to improve functional status in patients with chronic heart failure^[62].

Controversial data exist regarding pharmacologic interventions in heart failure: some antidiabetic medications raise safety concerns in these patients, while heart failure medication that has been shown to improve clinical outcomes may be associated with the development of new-onset diabetes. We will review the latest evidence in pharmacologic interventions that can reverse insulin resistance in this specific population.

ACEIs and ARBs

The use of ACEIs and ARBs has been reported to significantly reduce the incidence of new-onset diabetes in large heart failure trials^[17,18]. In the SOLVD program, enalapril significantly reduced the incidence of diabetes in patients with left ventricular dysfunction, mainly in those with impaired fasting plasma glucose^[17]. Furthermore, enalapril was the greatest predictor for a lower risk of developing diabetes in the multivariate analysis. In the CHARM-Preserved study in patients with chronic heart failure and preserved ejection fraction, treatment with candesartan was associated with a 40% reduction in the development of newly-diagnosed diabetes, and in other subgroups of the CHARM study the decline was 22%^[18]. Overall, the results of this subanalysis suggest that renin-angiotensin system blockade with ACEIs or ARBs prevents the development of DM in patients with chronic heart failure. However, in a clinical trial designed to evaluate the effect of telmisartan and candesartan on insulin sensitivity in patients with heart failure, no significant changes in insulin sensitivity were observed after 5 months of treatment^[28]. In the Diabetes Reduction Assessment with Ramipril or Rosiglitazone Medication (DREAM) study, ramipril treatment did not significantly lower the incidence of new-onset diabetes in patients with impaired fasting glucose^[63]. However, in the Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) study^[64], valsartan modestly reduced the incidence of DM. These differences in the reduction of incident diabetes and insulin resistance could be due to aldosterone escape that could affect their efficacy^[65-67]. The meta-analysis of Andraws *et al*^[68] proved that renin-angiotensin system drug inhibition may prevent the onset of DM. Specifically, in ACEI trials, the reduction in the risk of developing DM was 28%, and 27% in the ARB trials.

Beta-blockers

Beta-blockers have a different effect on lipid and glucose metabolism according to their receptor specificity. Several studies have reported that first-generation beta-blockers increased the risk of diabetes after 10 years of treatment^[69]. The ARIC Study showed that propranolol and timolol raised the diabetes risk by 28%^[70]. In contrast, second-generation beta-blockers such as atenolol and metoprolol, among others, have been associated with 13% and 20% reductions in insulin sensitivity, respectively^[34,71]. Finally, third generation beta-blockers, such as dilevalol, carvedilol and celiprolol which combine properties of nonselective beta-blockers with other effects such as vasodilatation and protection against oxidation, usually increase insulin sensitivity and improve the lipid profile. In a study of 72 non-diabetic patients, insulin sensitivity dropped by 14% after 12 weeks of treatment with metoprolol compared with an increase of 9% in those who continued treatment with carvedilol^[72]. In the COMET study^[19], carvedilol was

associated with a reduced incidence of new-onset DM in patients with chronic heart failure compared with metoprolol. Furthermore, non-selective beta-blockers such as nebivolol and carvedilol that do not worsen insulin sensitivity appear to exert beneficial effects on heart failure^[73]. Nebivolol also inhibits the angiotensin II-induced activation of NADPH oxidase and reactive oxygen species, thereby providing a rationale for its exerting beneficial effects on insulin sensitivity^[74].

Thiazolidinediones

Thiazolidinediones are peroxisome proliferator-activated (PPAR- γ) receptor agonists that modulate the transcription of insulin-sensitive genes involved in the control of glucose and lipid metabolism in adipose tissue, muscle and liver. It is recognized that they improve insulin sensitivity and reduce free fatty acids; however, as a result of their effects on renal sodium reabsorption and vascular permeability, they cause fluid retention, edema and weight gain, thereby raising the risk of heart failure^[75].

The European Society of Cardiology (ESC) 2012 guidelines for the diagnosis and management of heart failure included thiazolidinediones on the list of treatments not recommended^[76]. Similarly, in accordance with American College of Cardiology Foundation/American Heart Association (ACCF/AHA) 2013 guidelines, thiazolidinediones adversely affect the clinical status of patients with current or previous symptoms of heart failure with reduced ejection fraction and should be avoided or withdrawn whenever possible^[77].

Metformin

It is known that the use of metformin prevents progression to new-onset DM in patients with prediabetes^[60]. Until recently, metformin was contraindicated in heart failure patients; however, heart failure patients on metformin have better outcome than those treated otherwise^[78-81]. A systematic review of observational studies involving 34,000 patients with DM and heart failure on metformin indicated that this medication is at least as safe as other glucose-lowering treatments in patients with DM and heart failure, and even in those with reduced left ventricular ejection fraction or concomitant chronic kidney disease^[82]. In a randomized controlled trial in 62 heart failure patients with insulin resistance to receive metformin or placebo for a period of 4 months, Wong *et al*^[83] analyzed the effect on exercise capacity. Although no enhancement of exercise capacity measured by peak oxygen uptake was observed, metformin treatment significantly improved insulin resistance with a favorable safety profile. Recently, metformin was shown to prevent the development of chronic heart failure in a hypertensive insulin-resistant rat model^[84]. Thus, in view of this evidence, metformin use appears to be safe and may be beneficial in chronic heart failure patients. Nevertheless, prospective randomized studies are required to ascertain the benefits of metformin treatment in patients with heart failure.

Incretin-based therapies

Incretin-based therapy such as glucagon-like peptide-1 (GLP-1) receptor agonists and dipeptidyl-peptidase-4 (DPP-4) inhibitors, in addition to the benefits of tight glycemic control, has independent cardioprotective effects that might also provide a novel treatment strategy for patients with insulin resistance and heart failure^[85]. A recent meta-analysis confirmed the cardiovascular safety of GLP-1 receptor agonists, at least in the short term and in low-risk individuals^[86]. Two main findings of the potential benefits of GLP-1 agonists in heart failure stem from the meta-analysis of Munaf

et al^[87]. Firstly, preclinical studies on different animal models showed favorable functional effects of GLP-1 in failing hearts, with significant improvements in left ventricular systolic and diastolic function. Secondly, the four clinical studies included in this meta-analysis also showed enhanced left ventricular contractile function in patients with chronic heart failure, but without improvement in B-type natriuretic peptide levels. The small sample sizes and non-randomized nature of these studies are the main limitations.

Regarding DPP-4 inhibitors, two meta-analyses confirmed their cardiovascular safety, at least in the short and medium term^[88,89]. Of the four large prospective randomized trials with cardiovascular outcomes, two are ongoing^[90,91] and two have been completed. Among the latter, the rates of major adverse cardiovascular events with alogliptin treatment in DM patients who had suffered an acute coronary syndrome were not increased compared with placebo^[92]. Further analysis of the EXAMINE trial showed that new-onset heart failure and hospitalizations for heart failure were not increased with alogliptin compared with placebo^[93]. Contradictory data were reported in the Saxagliptin Assessment of Vascular Outcomes Recorded (SAVOR) study^[94], despite not affecting cardiovascular event rates, saxagliptin was associated with a 27% increase in the risk of hospitalization for heart failure. Therefore, we do not currently have enough evidence to support the use of incretin-based therapies to improve insulin sensitivity in patients with chronic heart failure.

CONCLUSIONS

The relationship between heart failure and DM is bidirectional. Although DM is a recognized risk factor for the development of heart failure, the association between heart failure and DM development has been less explored and the underlying pathophysiologic explanation remains to be clarified. Chronic heart failure is an insulin resistance state and the degree of insulin resistance is associated with disease severity and prognosis. Among the pathophysiologic mechanisms that may explain the association between heart failure and insulin resistance, the most accepted are sympathetic overactivity, increased circulating free fatty acid concentration and adiponectin resistance. Pharmacologic and non-pharmacologic strategies to improve insulin sensitivity must be considered in the clinical management of patients with heart failure although further studies are required to assess their efficacy and safety (Table 1).

Table 1 Heart failure and insulin resistance/diabetes: Key messages.

Chronic heart failure is associated with an insulin resistance state and an increased incidence of DM.
Insulin resistance contributes adversely to the progression of heart failure. There is a pathophysiologic link between chronic heart failure and insulin resistance.
Insulin resistance could be a therapeutic target in chronic heart failure patients.
Renin-angiotensin system inhibition by ACEIs or ARBs may prevent the onset of DM.
Third generation beta-blockers that combine properties of nonselective beta-blockers with vasodilator and antioxidant effects usually increase insulin sensitivity.
Thiazolidinedione therapy is not recommended in heart failure patients.
Insulin-resistant patients with heart failure stand to benefit from metformin use.
Effects of incretin-based therapy on heart failure outcomes should be tested in dysglycemic patients.

CONFLICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

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