LEADING ARTICLE

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Impaired Glucose Metabolism in Patients with Heart Failure

Pathophysiology and Possible Treatment Strategies

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Abstract

The firm association of diabetes mellitus with congestive heart failure (CHF) has been undoubtedly established. Recent reports support the presence of the reciprocal interrelationships between CHF and glucose abnormalities. The present review provides an overview of some aspects of the multifactorial interrelationships between heart failure and diabetes mellitus. Patients with heart failure are generally at higher risk of developing type 2 diabetes mellitus. Several factors may be involved, such as a lack of physical activity, hypermetabolic state, intracellular metabolic defects, poor muscle perfusion, and poor nutrition. **((Author: Blood/Plasma/Serum?))** levels of inflammatory cytokines and leptin are elevated in patients with heart failure. Activation of the sympathetic system in CHF not only increases insulin resistance but also decreases the release of insulin from the pancreatic β cells, increases hepatic glucose production by stimulating both gluconeogenesis and glycogenolysis, and increases glucagon production and lipolysis. People who develop type 2 diabetes mellitus usually pass through the phases of nuclear peroxisome proliferator-activated receptor (PPAR) modulation, insulin resistance, hyperinsulinemia, pancreatic β-cell stress and damage leading to progressively decreasing insulin secretion, and impaired fasting and postprandial blood glucose levels. Once hyperglycemia ensues, the risk of metabolic and cardiovascular complications also increases. It is possible that the cornerstone of diabetes mellitus prevention in patients with CHF could be controlled by increased physical activity in a cardiac rehabilitation framework. Pharmacologic interventions by some medications (metformin, orlistat, ramipril and acarbose) can also effectively delay progression to type 2 diabetes mellitus in general high risk populations, but the magnitude of the benefit in patients with CHF is unknown. In patients with CHF and overt diabetes mellitus, ACE inhibitors may provide a special advantage and should be the first-line agent. Recent reports have suggested that angiotensin receptor antagonists, similar to ACE inhibitors, provide beneficial effects in patients with diabetes mellitus and should be the second-line agent if ACE inhibitors are contraindicated. Treatment with HMG-CoA reductase inhibitors should probably now be considered routinely for all diabetic patients with CHF, irrespective of their initial serum cholesterol levels, unless there is a contraindication.

Coronary artery disease (CAD) is the leading cause of congestive heart failure (CHF)**((Author: heart failure has been replaced with CHF throughout text, please confirm))** in the population.[1] Paradoxically, the prevalence of CHF appears to be escalating, despite a decline in CAD mortality.[2-6] Recently, a prominent worldwide increase in type 2 diabetes mellitus has also been demonstrated.[7-11] Patients with diabetes mellitus have not experienced the reduction in cardiac mortality rates that has been demonstrated in nondiabetic patients.[12] Several epidemiologic reports have shown that diabetes mellitus is a direct independent risk factor for the development of CHF.[13-17] The firm association of diabetes mellitus and glucose abnormalities with cardiovascular morbidity and mortality has been undoubtedly demonstrated.[9,18-21]

The current American Diabetes Association (ADA) criteria have specified a new category of abnormal glucose metabolism: impaired fasting glucose (IFG) [blood glucose levels of 110–125 mg/dL].[22] The substantially increased mortality rate among pa-

tients with IFG and the association of this condition with prevalence of CHF was also described.[18,23,24]

An insulin-resistant state constitutes the major risk factor for the development of diabetes mellitus.[25,26] Evidence is increasing that in some populations, type 2 diabetes mellitus shares common causal factors with cardiovascular disease and, in particular, with CAD.[19] In turn, CHF is also related to markedly increased insulin resistance, characterized by both fasting and stimulated hyperinsulinemia.[20,21]

Moreover, recent reports support the presence of the reciprocal interrelationships between CHF (in terms of decreased functional capacity) and glucose abnormalities.[27-31]

The present review provides an overview of some aspects of the multifactorial interrelationships between CHF and diabetes mellitus.

1. Diabetes Mellitus Leads to Congestive Heart Failure (CHF)

Diabetes mellitus is a frequent comorbidity in patients with CHF. In major clinical trials, diabetes mellitus was observed in 20–38% of patients with CHF.[27-29] Diabetes mellitus markedly increases the likelihood of CHF in patients without established cardiac disease. The Framingham study was the first to show an increased risk of CHF in patients with diabetes mellitus, with an incidence of CHF that showed a 4-fold and 8-fold increase in men and women with diabetes mellitus, respectively, compared with those without diabetes mellitus.[13] In the National Health and Nutrition Examination Survey (NHANES), diabetes mellitus was independently associated with an increased risk of CHF (relative risk [RR] 1.85; 95% CI 1.51, 2.28; $p < 0.01$).[14] The association between plasma glycosylated hemoglobin (HbA_{1c}) levels and the incidence of CHF was studied in a large, population-based sample of adult patients (29 958 men and 22 900 women) with diabetes mellitus with no known history of CHF observed for a median duration of 2.2 years. After adjustment for other risk factors, concomitant therapy, and type and duration of diabetes mellitus, a significant independent association was found between plasma HbA_{1c} levels and incidence of CHF. Each 1% increase in its level was associated with an 8% increase in the risk of hospitalization or death due to CHF. A plasma HbA_{1c} level ≥10%, relative to HbA_{1c} <7%, was associated with a 1.56-fold (95% CI 1.26, 1.93) greater risk of CHF.[31]

Diabetes mellitus is not only a risk factor for CHF in patients without structural heart disease, but it is also associated with a worse outcome once a cardiac disease (e.g. a myocardial infarction or CHF itself) has developed. A report from the Studies of Left Ventricular Dysfunction (SOLVD) trial had identified diabetes mellitus as an independent risk factor of increased mortality and morbidity in both symptomatic and asymptomatic patients with CHF.[32,33] Diabetes mellitus is also associated with an increased risk of CHF and death in patients with an acute myocardial ischemic event.[34,35] Many mechanisms may explain both the increased incidence of CHF in patients with diabetes mellitus without any initial cardiac disease and the worse outcome of patients with diabetes mellitus in whom a cardiac disease has developed.[27,34-37]

Population-based studies have demonstrated an increased left ventricular mass and wall thickness with subclinical impairment in left ventricular systolic function, shown by a lower left ventricular fractional shortening, midwall shortening and stress-corrected midwall shortening, and increased arterial stiffness in patients with diabetes mellitus, compared with those without diabetes mellitus.[38] Diabetes mellitus likely acts on the intrinsic properties of the myocardium with an effect that is independent and additive to the more common and widespread CAD and to the associated abnormalities of autonomic function, with increased sympathetic and decreased vagal stimulation.[27,34,37] Accordingly, histology studies have shown that diabetes mellitus is associated with myocyte hypertrophy, perivascular fibrosis, and an increase in matrix collagen, cellular triglycerides, and cell membrane lipids, consistent with nonenzymatic glycation of vascular and membrane proteins, increased cellular fatty acid uptake, and hyperglycemia-induced oxidative stress.[36] Abnormalities of left ventricular diastolic function with a reduced left ventricular compliance occur early in the course of diabetes mellitus, even before hypertension, vasculopathy, and fasting hyperglycemia have developed, suggesting that they are secondary to diabetes mellitus.[39] Metabolic abnormalities may also explain the unfavorable synergy observed between diabetes mellitus and CAD in patients with CHF. The impaired glucose uptake caused by diabetes mellitus may, in fact, be particularly deleterious in patients with concomitant CAD, which is, in turn, generally associated with a shift in myocardial metabolism from free fatty acids to glucose and glycolysis.[27,33] It is therefore clear how the treatment of diabetes mellitus should reduce both the incidence of new cases of CHF and the morbidity and mortality of patients in whom CHF has already developed. Glycemic and HbA_{1c} serum levels should be controlled and reduced to normal levels, even with the possibility of untoward effects from intensive insulin treatment.[16] Tighter BP control with reduction of BP to <130/80mm Hg has been shown to be associated with a reduced risk of CHF in the UK Prospective Diabetes Study (UKPDS).[40] In addition, ACE inhibitors can prevent the development of major cardiovascular events and CHF in patients with diabetes mellitus, even when they do not have concomitant hypertension.[41-43]

2. Glucose Metabolism and CHF: Reciprocal Interrelationship

In general populations, increased body mass index (BMI), pre-existing glucose and insulin abnormalities, advanced age, physical inactivity, and parental diabetes mellitus appear to be acknowledged risk factors for the development of new diabetes mellitus.[44-47] Other potential risk factors (e.g. hypertension, diuretic use, hypertriglyceridemia, hyperuricemia and absence of alcohol intake) have been widely discussed.[47-49] Several studies that sought to determine whether patients with CHF are in fact more insulin resistant than those without CHF have left little doubt that CHF is an 'insulin-resistant state'.[50,51] For this reason, patients with CHF are generally at higher risk of developing type 2 diabetes mellitus. Whether patients with more advanced myocardial dysfunction have more severe insulin resistance has not been demonstrated with certainty, although the relation is likely. Although the mechanisms for the greater insulin resistance in these patients are not entirely known, the literature suggests that several mechanisms are likely to be involved.[52] Patients with CHF usually diminished their exercise activity. An inverse relationship between physical activity level and the risk of subsequent type 2 diabetes mellitus, has also been described.[49,53,54] Therefore, the thesis that patients with CHF are prone to develop new diabetes mellitus seems to be based on a reliable theoretic background and has been stressed in some reviews.[27,28,55,56]

In the past, the potential prodiabetic effect of the significantly decreased functional status in patients with CHF might have been negligible due to their relatively short life expectancy. Following the implementation of new treatment regimens (mainly ACE inhibitors, aspirin, and β-adrenoceptor antagonists), the life expectancy of patients with CHF has increased during recent decades. Therefore, the development of new diabetes mellitus is becoming a relevant issue for clinical practice as a potential reservoir for reducing the risk of morbidity and mortality among the cardiac patients. These data are in keeping with Omran's concept of the ongoing epidemiologic transition:[57,58] The epoch of long-term survival for patients with CHF, that can allow development of new diabetes mellitus, is just coming now.

The Osservatorio Geriatrico Regione Campania Group study has directly investigated the significance of CHF in the prediction of future development of diabetes mellitus in 1339 elderly patients with a mean age of 74.2 ± 6.4 years.[59] When untreated CHF patients were grouped into those with low (I and II) and high (III and IV) New York Heart Association (NYHA) functional classes, the association of CHF and diabetes mellitus was stronger with the worsening of CHF. In a longitudinal study, CHF predicted diabetes mellitus independently of age, sex, family history of diabetes mellitus, BMI, waist/hip ratio, SBP and DBP, and therapy for CHF (odds ratio 1.4; 95% CI 1.1, 1.8). The investigators hypothesized that elevated serum free fatty acid (FFA) concentrations might play a pivotal role. In the Bezafibrate Infarction Prevention (BIP) study in patients with CAD, NYHA class III was associated with a 1.7-fold (95% CI 1.1, 2.6) increase in the rate of development of diabetes mellitus**((Author: ?, compared with NYHA class I,))** during a 6- to 9-year follow-up[60] (figure 1).

Usually, hyperglycemia found in patients with CAD undergoing routine fasting blood glucose (FBG) analyses throughout follow-up observation, is defined as 'undiagnosed diabetes mellitus'. However, it seems unlikely that diabetes mellitus would remain undiagnosed in a large number of patients who underwent multiple hospital and out of hospital examinations. Based on the BIP study data, we suggest that the problem of undiagnosed diabetes mellitus among the 'well characterized' CAD patients, in contrast to the general population, is a problem of newly developed but not 'missed on screening' diabetes mellitus.

FBG levels are determined principally by two major factors: insulin-secretion capacity and insulin resistance in peripheral tissues. An additional and important, but probably relatively less influential factor is hepatic glucose production. An insulin-resistant state constitutes the major risk factor for the development of diabetes mellitus. Hyperinsulinemia appears to be a compensatory mechanism that responds to increased levels of circulating glucose. People who develop type 2 diabetes mellitus usually pass through the phases of nuclear peroxisome proliferator-activated receptor (PPAR) modulation, insulin resistance, hyperinsulinemia, pancreatic β-cell stress and damage leading to progressively de-

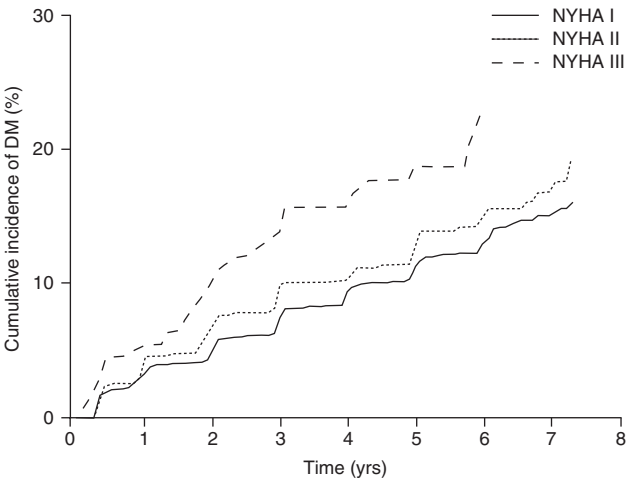

Fig. 1. Kaplan-Meier curves of the incidence of diabetes mellitus (DM), in accordance with the time of diagnosis following annual fasting blood glucose measurements, for the study groups in New York Heart Association (NYHA) functional classes I, II, and III (reproduced from Tenenbaum et al.,[60] with permission).

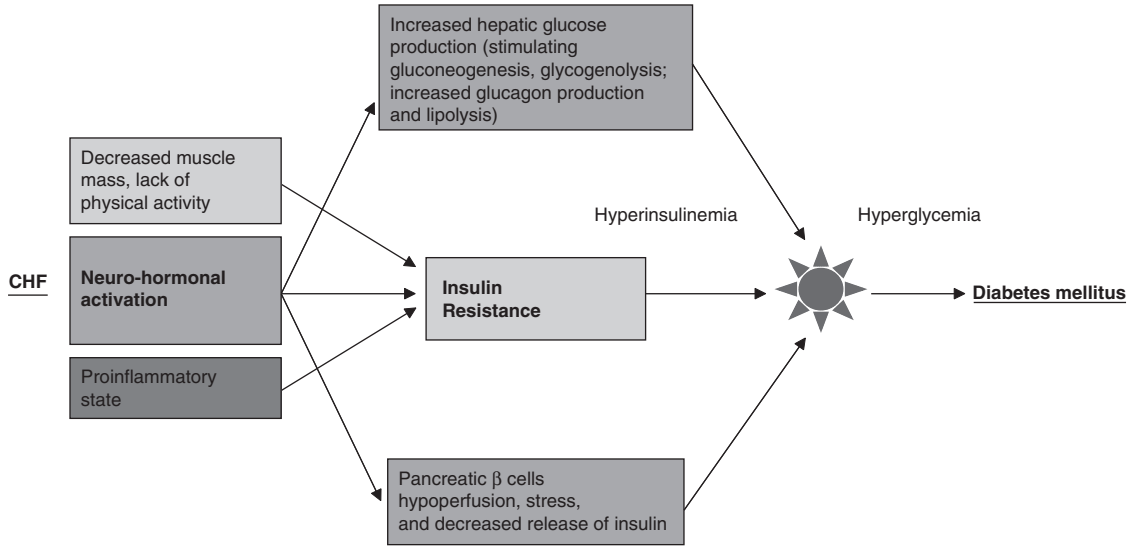

Fig. 2. The relationship between chronic**((Author: ?replace with congestive as in text))** heart failure (CHF), insulin resistance, hyperinsulinemia and hyperglycemia (overt type 2 diabetes mellitus). An insulin-resistant state is the key event in the initiation of glucose metabolism abnormalities. Afterwards, there are two possible scenarios for progression of glucose metabolism abnormalities: (i) with substantial injury of pancreatic β cells (lower arrows) leading to the gradual reduction of insulin secretion and to hyperglycemia (e.g. overt type 2 diabetes mellitus). Additional mechanisms (upper arrows) contributing to hyperglycemia may be related to increased hepatic glucose production; and (ii) with preserved pancreatic β-cell function and insulin hypersecretion (hyperinsulinemia), which can compensate for insulin resistance for a long time**((Author: can this be made more specific? e.g. several months?))** without hyperglycemia (this pathway is not shown).

creasing insulin secretion, and impaired postprandial and FBG levels.[61-65] FBG is presumed to remain normal as long as insulin hypersecretion can compensate for insulin resistance. The decrease in insulin secretion leading to hyperglycemia occurs as a late phenomenon and, in fact, separates the patients with insulin resistance from those with or without overt diabetes mellitus (figure 2).

The predominant factors affecting insulin sensitivity in the general population without CHF are body fat content and distribution. However, advancing CHF is not accompanied by increasing adiposity. For one thing, appetite appears to be suppressed in patients with severe CHF. In fact, weight loss is common in such patients, and some even develop cardiac cachexia.[66] In addition, CHF appears to be accompanied by a hypermetabolic state in which energy expenditure at rest is increased. This state may be partially related to increased breathing efforts or defects in intracellular metabolism and may be a consequence of hypoperfusion of organs. Furthermore, patients with CHF show elevated serum levels of leptin and its soluble receptor. It was suggested that elevated leptin levels directly and independently predict insulin resistance. Therefore, leptin may participate in the catabolic state leading to the development of cardiac cachexia in the course of CHF.[67] At the same time, lack of physical activity in patients with severe CHF should lead to decreased muscle mass.[68] Muscle is the major site of glucose utilization, and thus a loss of muscle mass increases insulin resistance. Several factors may be involved, such as a lack of physical activity, hypermetabolic state, intracellular metabolic defects, poor muscle perfusion, and poor nutrition. Decreased muscle mass impairs muscle utilization of glucose, which reduces sensitivity to insulin. It can be expected that muscle loss accompanied by a worsening of the metabolic state will be greatest in patients with severe CHF.

Another cause of insulin resistance may be a proinflammatory state.[69] Plasma levels of inflammatory cytokines are elevated in patients with CHF. These cytokines seemingly contribute to cachexia. Indeed, one cytokine tumor necrosis factor-α was initially called cachectin.[70] High levels of cytokines have been reported to interfere with insulin action, which worsens insulin resistance.

Whether advancing CHF is accompanied by a decrease in insulin secretory capacity has not been accurately determined. In view of the general deterioration of cellular function and poor organ perfusion with worsening CHF, however, such an association may be possible. Moreover, impaired myocardial performance results in activation of the neurohormonal compensating systems, including activation of the sympathetic nervous system to avoid systemic hypoperfusion with the degree of sympathetic activation being proportional to the severity of ventricular dysfunction and functional class of CHF.[71] Activation of the sympathetic system not only increases insulin resistance but also decreases the release of insulin from the pancreatic β cells, increases

Table I. Mechanisms likely to be involved in the development of hyperglycemia and diabetes mellitus in patients with congestive heart failure

Insulin resistance in peripheral tissues	Decreased pancreatic release of insulin	Increased hepatic glucose production
Decreased muscle mass	General deterioration of cellular function	Gluconeogenesis
Lack of physical activity	Poor organ perfusion	Glycogenolysis
Elevated leptin levels	Sympathetic activation	Increased glucagon production
Hypermetabolic state (energy expenditure is increased)	Higher catecholamine levels	Lipolysis
Intracellular metabolic defects		
Poor muscle perfusion		
Poor nutrition (suppressed appetite)		
Proinflammatory state		
Neurohormonal activation		

hepatic glucose production by stimulating both gluconeogenesis and glycogenolysis and increases glucagon production and lipolysis.[72-75] Therefore, higher catecholamine levels can be an additional reason for the increased development of diabetes mellitus in patients with a lower functional class of CHF (table I). It should be emphasized, the true role of leptin, inflammatory cytokines, and catecholamines in CHF is far from clear and still controversially discussed in the literature.[76-79]

Once hyperglycemia ensues, the risk of metabolic and cardiovascular complications also increases. Although patients with severe CHF may still not live long enough to experience all the long-term detrimental effects of chronic hyperglycemia, they will be at risk of the more immediate complications, such as hyperosmolar coma, infection, and, possibly, worsening CHF.

3. Prevention of Diabetes Mellitus

Because of its critical and central role in the development of type 2 diabetes mellitus and many cardiovascular disorders, we believe that targeted treatment of PPAR (both α and γ) will be a critical component of diabetes care in the near future (figure 3). Currently, PPAR-related treatment could theoretically be based on lifestyle interventions, fibric acid derivatives (PPAR-α ligands), and the thiazolidinedione group of insulin-sensitizing drugs (PPAR-γ ligands). It is possible that the cornerstone of diabetes prevention in patients with CHF will be controlled, increased physical activity in a cardiac rehabilitation framework. An inverse relationship between the level of physical activity and the risk of subsequent type 2 diabetes mellitus has been described.[53,54] The Diabetes Prevention Program (DPP) results have shown that individualized, systematic, and intensive lifestyle interventions (including dietary changes and increased physical activity) are the most effective means of prevention of type 2 diabetes mellitus in general high risk populations.[50-82] **((Author: should this be** [80-82]**, or** [50,82]**, or is** [50-82] **correct?))**In addition, pharmacologic interventions by some medications which influence primary glucose metabolism (metformin and acarbose) can effectively delay progression to type 2 diabetes mellitus in general high risk populations,[83-85] but the magnitude of the benefit seems to be somewhat less (58% for DPP lifestyle changes vs 31% for metformin and 25% for acarbose).

Cigarette smoking is an additional and important modifiable risk factor that could be targeted for prevention of diabetes mellitus. A number of previous epidemiologic studies found smoking to be positively associated with risk for type 2 diabetes mellitus.[86-88] These data strongly support the overwhelming importance of smoking cessation in a framework of secondary prevention policy in patients with CAD and decreased functional capacity.

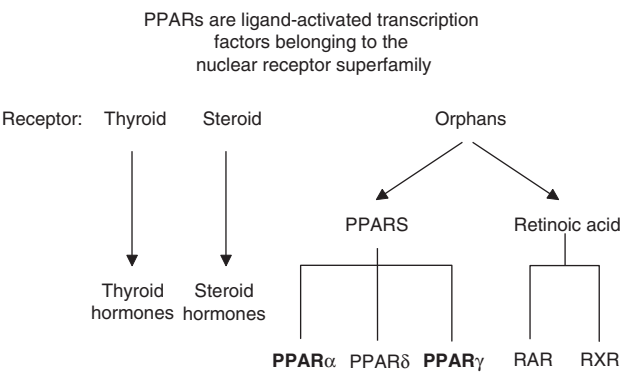

Fig. 3. The peroxisome proliferator-activated receptors (PPARs) in the framework of the nuclear receptor superfamily. **RAR** = retinoic acid receptor; **RXR** = retinoid X receptor.

4. Cardiovascular Risk Factors: Pharmacologic Intervention in CHF and Overt Diabetes Mellitus

4.1 Hypertension

Patients with diabetes mellitus and hypertension frequently develop CHF and renal insufficiency. The prevalence of hypertension in patients with diabetes mellitus is considerably higher than in nondiabetic individuals.[89-94] Although the origin of hypertension is multifactorial, the causal link between insulin resistance and hypertension is growing.[89-94] The UKPDS has shown that lowering BP by 10mm Hg systolic and 5mm Hg diastolic significantly reduces the incidence of stroke (44%; p = 0.013), diabetes-related death (32%; p = 0.019), and microvascular complications (37%; p = 0.0092) in patients with type 2 diabetes mellitus.[40] Similar results were obtained in the Hypertension Optimal Therapy (HOT) study, which showed a 51% (p < 0.005) cardiovascular risk reduction in patients with diabetes mellitus, with a goal DBP of 80mm Hg, and the Systolic Hypertension in Europe (Syst-Eur) trial, which showed a 63% risk reduction by lowering SBP by 10mm Hg.[95,96]

BP control in patients with diabetes mellitus has been a challenge, with most patients requiring more than **((Author: ?at least))**two agents to achieve optimal BP control.[97] The choice of antihypertensive agents has been well studied in various randomized control trials. ACE inhibitors, diuretics, β-adrenoceptor antagonists and calcium channel antagonists have been studied. The Appropriate Blood Pressure Control in Diabetes (ABCD), Fosinopril Versus Amlodipine Cardiovascular Events Randomized Trial (FACET), Captopril Prevention Project (CAPP), Swedish Trial in Old Patients with Hypertension-2 (STOP-2) and Heart Outcomes Prevention Evaluation (HOPE) studies have without doubt shown the cardioprotective effect of ACE inhibitors and their benefit in the treatment of hypertension in patients with diabetes mellitus.[94,98-101] The HOPE study showed that using the ACE inhibitor ramipril in patients who already had a BP of 139/79mm Hg further reduced cardiovascular death by 37% (p = 0.0001).[94] Pahor et al. performed a meta-analysis of randomized controlled trials that included patients with type 2 diabetes mellitus and hypertension who were randomized to an ACE inhibitor or an alternative drug (nisoldipine in the ABCD trial, diuretics or β-adrenoceptor antagonists in the CAPP trial, amlodipine in the FACET trial and atenolol in the UKPDS trial).[102] The cumulative results of the first three trials showed a significant benefit of ACE inhibitors compared with alternative treatments on the outcomes of acute myocardial infarction (63% reduction; p < 0.001), cardiovascular events (51% reduction; p < 0.001), and all-cause mortality (62% reduction; p = 0.010), which was not seen in the UKPDS trial. None of the findings were explained by differences in BP control, suggesting that ACE inhibitors may provide a particular advantage in patients with CHF in addition to BP control.

Early and aggressive treatment with ACE inhibitors reduces cardiovascular complications and development of renal failure in patients with diabetes mellitus. ACE inhibitors should be the first-line agent in the treatment of hypertension in patients with diabetes mellitus, both with and without CHF, unless there is a contraindication. Recent reports have suggested that angiotensin receptor antagonists [103] similar to ACE inhibitors,[94] provide renoprotective effects in patients with diabetes mellitus. Recent data from the Losartan Intervention For Endpoint reduction in hypertension (LIFE) trial indicate that losartan was significantly more effective than the β-adrenoceptor antagonist atenolol in reducing cardiovascular morbidity and death in hypertensive patients with left ventricular hypertrophy.[104] Indeed, patients receiving losartan were less likely to develop type 2 diabetes mellitus during the study, and a separate analysis of patients with diabetes mellitus showed a reduced risk of cardiovascular mortality. However, due to the methodologic flaws and the incomplete data in the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study, the question of the effectiveness and safety of this drug in the specific setting of patients with diabetic nephropathy remains yet unanswered.[105,106] For the time being, angiotensin receptor antagonists should still be considered second-line agents in the treatment of hypertension in patients with diabetes mellitus, for use in patients in whom ACE inhibitors are contraindicated.**((Author: should reference [107] be cited here?))**

4.2 Lipids

Lipid abnormality is a major problem in patients with diabetes mellitus. Among patients with diabetes mellitus, 97% had at least one lipid abnormality.[108] However, only 9% were taking lipid-lowering agents. Among those who were treated, only 1% had serum low density lipoprotein-cholesterol (LDL) levels <100 mg/dL. Similar results were also noted in the Lipid Treatment Assessment Project (L-TAP).[109] The Multiple Risk factor Intervention Trial (MRFIT) has shown that at every cholesterol level, patients with diabetes mellitus had a 2- to 3-fold increase in cardiovascular disease compared with those who did not have diabetes mellitus.[110] Patients with diabetes mellitus and CHF may not have higher serum LDL-C levels than those without diabetes mellitus. However, the LDL particle in patients with diabetes mellitus, being smaller, denser and highly oxidized, is more atherogenic.[111] In addition, patients with type 2 diabetes mellitus also have elevated serum levels of triglycerides and very low density lipoprotein-cholesterol (VLDL-C) and decreased serum levels of high

density lipoprotein-cholesterol (HDL-C), which are additional risk factors for cardiovascular disease.[112] Subgroup analysis of various randomized control trials have shown a significant reduction in cardiovascular events in patients with diabetes mellitus and hyperlipidemia who were treated with HMG-CoA reductase inhibitors or fibric acid derivatives.[113-116]

HMG-CoA reductase inhibitors have shown benefit not only in primary but also in secondary prevention of cardiovascular events. A *post hoc* study of the patients in the Scandinavian Simvastatin Survival Study (4S) trial showed that simvastatin-treated patients with diabetes mellitus had significantly reduced numbers of major coronary events (RR 0.58; p = 0.001) and revascularizations (RR 0.52; p = 0.005). Total mortality (RR 0.79; p = 0.34) and coronary mortality (RR 0.72; p = 0.26) were also reduced in diabetes mellitus, although not significantly. In prediabetic IFG patients, simvastatin use significantly reduced the number of major coronary events (RR 0.62; p = 0.003) and revascularizations (RR 0.57; p = 0.009).[117] HMG-CoA reductase inhibitors also have an anti-inflammatory effect and improve endothelial function. In a randomized study of patients with type 2 diabetes mellitus, patients treated with atorvastatin for 6 months showed a decrease in plasma C-reactive protein (CRP) levels ($p < 0.05$) and improved endothelium-dependent vasodilation ($p < 0.05$) compared with patients treated with placebo.[118] All these trials show that aggressive screening and management of lipid abnormalities is essential in patients with diabetes mellitus in order to slow the progression of cardiovascular disease, including CHF.

The desirable serum level of LDL-C in patients with diabetes mellitus is still being debated. However, the American Diabetic Association (ADA) and the National Cholesterol Education Program Adult Treatment Panel III guidelines indicate a target LDL-C level of <100 mg/dL, a target HDL-C level of >45 mg/dL in men and >55 mg/dL in women, and a target triglyceride level of <150 mg/dL for individuals with diabetes mellitus.[12,119] **((Author: ?is ref [12] the correct reference. Also, please add mention of the revised NCEP ATP III recommendations from Circulation 2004; 110: 227-39))** In accordance with recent Medical Research Council/British Heart Foundation Heart Protection Study (HPS) of cholesterol-lowering with simvastatin, HMG-CoA reductase inhibitor therapy should now be considered routinely for all patients with diabetes mellitus at sufficiently high risk of major vascular events, irrespective of their initial serum cholesterol levels.[120]

4.3 Homocysteine

Current data suggest elevated plasma homocysteine levels to be an independent risk factor for the development of atherosclerosis.[121,122] Homocysteine may work synergistically with diabetes mellitus in promoting accelerated atherosclerosis. Various studies have shown that patients with diabetes mellitus who also have hyperhomocystinemia have increased incidence of cardiovascular disease.[123-125] However, no controlled clinical trial has demonstrated a reduction in cardiovascular disease with decreasing plasma-homocysteine levels. Several such trials are underway, examining the effect of reducing the homocysteine level with vitamin supplementation (folic acid, pyridoxine [B_6], and cyanocobalamin [B_{12}]) on cardiovascular mortality and morbidity.[126] Since hyperhomocystinemia is an easily reversible condition with relatively inexpensive interventions, such as vitamin supplements, it may be theoretically considered in both primary and secondary prevention of cardiovascular disease in patients with diabetes mellitus. However, in a recently published study by Liem et al., folic acid does not seem to reduce clinical endpoints in patients with stable CAD while receiving statin treatment.[127] Thus, low dose folic acid supplementation should be treated with reservation until more trial outcomes become available.

4.4 Role of Aspirin in Diabetes Mellitus

The aggregation of platelets plays a major role in the progression of CAD in patients with diabetes mellitus. Platelets obtained from patients with diabetes mellitus show increased adhesiveness and an exaggerated aggregation, both spontaneous and in response to stimulating agents, such as thromboxane. Aspirin blocks the synthesis of thromboxane by irreversibly acetylating platelet cyclo-oxygenase and hence prevents the aggregation of platelets.[128-130] A recently published meta-analysis of 145 randomized trials showed that aspirin therapy protects against myocardial infarction, stroke, and death.[131] The ADA recommends that, in the absence of specific contraindications, aspirin should be (i) used for secondary prevention in men and women with evidence of large-vessel disease (myocardial infarction, vascular bypass procedure, stroke, transient ischemic attack, or angina pectoris); and (ii) be considered for primary prevention in adults who have one or more risk factors for cardiovascular disease (family history of CAD, smoking, hypertension, obesity, albuminuria, or lipid abnormalities) or who are **((Author: ?**≥**))**30 years of age.[132] In spite of this recommendation, aspirin is still underutilized in patients with diabetes mellitus.[133] The contraindications for aspirin use are aspirin allergy, bleeding tendency, recent gastrointestinal bleeding, and clinically active hepatic disease. Aspirin treatment is effective and inexpensive, and remains the treatment of choice in the prevention of CAD thrombotic complications in patients with diabetes mellitus. Medium dose aspirin (75–325 mg/day) is the most widely tested antiplatelet regimen and has the evidence of benefit with least toxicity.

4.5 Oral Antihyperglycemic Therapy

Five types of oral antihyperglycemic drugs are currently approved for the treatment of diabetes mellitus: biguanides, sulfonylureas, meglitinides, thiazolidinediones and α-glucosidase inhibitors. Except for thiazolidinediones, which will be considered separately, no particular concerns arise regarding the employment of these drugs in the context of patients with CHF.

The most widely used insulinotropic drugs are sulfonylureas. They block cardiac adenosine triphosphate-sensitive potassium (K_{ATP}) channels, and the opening of K_{ATP} channels is postulated to be involved in the genesis of ventricular arrhythmias in CHF.[134] In a multiple logistic regression in patients with severe CHF, this therapy was a negative predictor of repetitive ventricular beats (adjusted odds ratio 0.31; 95% CI 0.12, 0.78; p = 0.01). Thus, concomitant sulfonylurea therapy seems to offer beneficial effects by reducing the occurrence of complex ventricular ectopy in these patients.[134] Regarding the other insulinotropic group, meglitinides, no information is available in the context of CHF.[135]

Biguanides are established and well known insulin sensitizers. Metformin is nowadays the only drug belonging to this group currently available in most parts of the world. In CHF, classic recommendations include monitoring for the possible development of lactic acidosis.[136] **((Author: the correspondence by Misbin et al.[136] states that "On the basis of the reports received by the FDA, congestive heart failure has recently been included as a contraindication to metformin therapy"))**However, recent findings support the concept that patients with diabetes mellitus who are treated with metformin and who tolerate the drug well may continue taking it, even when mild renal impairment develops; this includes patients with CHF.[137]

The primary mechanism of action of α-glucosidase inhibitors (acarbose, voglibose, and miglitol) is based on the competitive inhibition of several enzymes of the α -glucosidase group (maltase, isomaltase, sucrase, and glucoamylase). These are membrane-bound enzymes that hydrolyze oligosaccharides and disaccharides to glucose in the brush border of the small intestine. Thus, by delaying the digestion of carbohydrates, these compounds shift their absorption to more distal parts of the small intestine and colon, and defer the gastrointestinal absorption of glucose. No influence on CHF was described for these drugs.[135] However, acarbose may interact with digoxin, leading to some reduction in its plasma levels.[138]

4.6 Thiazolidinediones and CHF

Thiazolidinediones are insulin sensitizers clinically used since 1997 and they bind to PPAR γ, leading to increased glucose transporter expression. Sensitivity to insulin, especially in adipocytes, muscle, and liver, is improved, and an additional major effect is the inhibition of hepatic gluconeogenesis.[139] It should be pointed out that no increment in insulin secretion is documented. There has been increasing discussion about the effects of thiazolidinediones on cardiac function, with evidence suggesting both negative and positive influences. A large proportion of patients with diabetes mellitus may have varying degrees of CHF, and there is considerable confusion about whether to initiate therapy.

Thiazolidinediones exert several effects on the heart and vasculature. These include effects on vascular resistance and afterload, left ventricular mass and contractility, neurohumoral regulation, ischemia and reperfusion, and myocardial metabolism.[140] Insulin-mediated vasorelaxation is blunted in patients with insulin resistance. Improving insulin sensitivity with thiazolidinediones may counter vascular insulin resistance and reduce hyperinsulinemia-induced endothelin-1 production, resulting in improved tonic vasodilator response to insulin and a reduction in peripheral vascular resistance and BP. Decreased peripheral resistance, in turn, may lead to increased stroke volume and cardiac output.[141]

Left ventricular hypertrophy is an important risk factor for CAD and cardiac-related mortality. The growth factor actions of insulin may lead to an exaggerated hypertrophic response of the left ventricle in response to arterial hypertension. In fact, the potent effects of ACE inhibitors on regression of left ventricular hypertrophy are related, in part, to their ability to improve insulin sensitivity.[142] It was suggested that the PPAR γ-dependent pathway plays a critical role in the inhibition of cardiac hypertrophy in response to *in vitro* and *in vivo* physiologic and pharmacologic stimulation.[143] However, clinical and echocardiographic studies with thiazolidinediones in patients with type 2 diabetes mellitus do not demonstrate a regression in cardiac hypertrophy.[144]

Insulin and insulin resistance have complex and interrelated effects on components of the neurohumoral cascade activated in patients with CHF. It is well accepted that increased sympathetic tone can induce insulin resistance, and conversely, hyperinsulinemia and insulin resistance promote increased sympathetic discharge. The renin-angiotensin system is activated progressively as cardiac function deteriorates, and inhibition of angiotensin-converting enzymes favorably remodels the myocardium in patients with CHF. A growing body of evidence suggests that thiazolidinediones counter angiotensin activation and thus exert a beneficial effect on ventricular remodeling in diabetic patients with CHF.[145] Evidence suggests that thiazolidinediones significantly reduce the production of tumor necrosis factor (TNF) α, a key factor in the development and progression of CHF.[146]

Thiazolidinediones may also exert beneficial effects in myocardial ischemia, and PPAR-γ agonists have been found to reduce

myocardial infarct size in experimental models of ischemia and reperfusion injury.[147] In addition, improving insulin sensitivity prevents the heart's reliance on free fatty acids as the primary source of energy by improving myocardial glucose use.[148]

The effects of thiazolidinedione treatment on nontraditional markers of cardiovascular disease in patients with type 2 diabetes mellitus should also be mentioned. Rosiglitazone reduces serum levels of matrix metalloproteinase-9 and the proinflammatory marker CRP in patients with type 2 diabetes mellitus, which indicates potentially beneficial effects on overall cardiovascular risk.[149]

Besides the above-mentioned favorable therapeutic aspects, there are concerns about whether thiazolidinediones have a detrimental effect on cardiac function. The majority of mechanistic and experimental studies would suggest that thiazolidinediones might favorably influence cardiac hemodynamics in CHF.[140] In contrast, large-scale clinical trials have reported fluid retention and increases in plasma volume (6–7%) with thiazolidinedione therapy, with an increased incidence of peripheral edema occurring in 2–5% of patients. Thiazolidinedione-induced peripheral edema and fluid retention is commonly refractory to diuretics and promptly responds to withdrawal of therapy.[150] However, a recent study found a response to diuretic therapy in some cases.[151] Thiazolidinedione-related pulmonary edema occurred 4–13 months after starting therapy,[152-154] although it has also been reported as early as 3 days after initiation of treatment.[153] The mechanism of edema formation has not been elucidated, but some evidence suggests that it may be related to increased endothelial cell permeability induced by thiazolidinedione therapy.[155]

In conclusion, countering insulin resistance with thiazolidinediones holds promise for cardiovascular risk reduction in patients with metabolic syndrome.[140] It is possible that early intervention with thiazolidinediones in these patients with preserved heart function may delay the development of CHF. However, in patients with some degree of CHF, the beneficial effects of thiazolidinediones may be offset by an increase in fluid volume and pulmonary edema. In such patients, therapy should be initiated with caution and promptly withdrawn with worsening CHF. These agents are contraindicated in patients with moderate to severe CHF (NYHA functional class III or IV).[135,140]

5. Conclusion

The firm association of diabetes mellitus with CHF has been undoubtedly established. Recent reports support the presence of the reciprocal interrelationships between CHF and glucose abnormalities. Patients with CHF are generally at higher risk of developing type 2 diabetes mellitus. Several factors may be involved, such as a lack of physical activity, hypermetabolic state, intracellular metabolic defects, poor muscle perfusion, and poor nutrition. Levels of inflammatory cytokines and leptin are elevated in patients with CHF. Activation of the sympathetic system in CHF not only increases insulin resistance but also decreases the release of insulin from the pancreatic β cells, increases hepatic glucose production by stimulating both gluconeogenesis and glycogenolysis, and increases glucagon production and lipolysis. Therefore, a relationship between CHF, insulin resistance, and overt diabetes mellitus exists independently from etiology of CHF (e.g. coronary atherosclerosis).

Patients who develop type 2 diabetes mellitus usually pass through the phases of nuclear PPAR modulation, insulin resistance, hyperinsulinemia, pancreatic β-cell stress and damage leading to progressive decrease of insulin secretion, and impaired postprandial and FBG levels. Once hyperglycemia ensues, the risk of metabolic and cardiovascular complications also increases. It is possible that the cornerstone of diabetes prevention in patients with CHF will be controlled, increased physical activity in a cardiac rehabilitation framework. Pharmacologic interventions by some medications (metformin, orlistat, ramipril, and acarbose) can also effectively delay progression to type 2 diabetes mellitus in general high risk populations, but the magnitude of the benefit in patients with CHF is unknown. In patients with CHF and overt diabetes mellitus, ACE inhibitors may provide a particular advantage and should be considered as first-line agents. Recent reports have suggested that angiotensin receptor antagonists, similar to ACE inhibitors, provide beneficial effects in patients with diabetes mellitus and should be the second-line agent if ACE inhibitors are contraindicated. HMG-CoA reductase inhibitor therapy should probably now be considered routinely for all diabetic patients with CHF, irrespective of their initial serum cholesterol levels, unless there is a contraindication.

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