Internal Medicine Grand Rounds

Cardiogenic Diabetes and Related Puzzles

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Because type 2 diabetes (T2D) and systolic left ventricular dysfunction (congestive heart failure, CHF) are common, it is not surprising that patients often suffer both conditions. The coexistence of these disorders is not merely overlap since coronary artery disease is associated with T2D, and these patients are more likely to develop CHF after myocardial infarction. T2D and hypertension are also closely related, so the simultaneous presence of both CHF and T2D is expected at a higher rate than predicted by their respective prevalence. For example, among the large scale trials of angiotensin converting enzyme inhibitors, the prevalence of diabetes was 20 - 25%, far higher than the prevalence of diabetes, 5 - 7%, in the adult population. The real prevalence of diabetes among patients with heart failure is likely even higher. Interestingly, the steadily expanding prevalence of CHF seems inconsistent with the decreasing prevalence of coronary disease and related improvements in care.

For a number of reasons it is likely that patients with both disorders will occupy an increasing fraction of an internist's practice in the near future. First, the prevalence of CHF is increasing, and diabetes may double within 25 years. Second, both disorders are associated with high morbidity. Third, like many chronic disorders, the prevalence of either T2D or CHF increases with age, often without overt clinical symptoms, but associated with other comorbid disorders. Finally, management of these patients is complex, often difficult and often time-consuming because of associated conditions and the need for polypharmacy with attendant risks of side effects. A number of the drugs proven valuable for one condition are contraindicated or discouraged for patients with the other condition, so the physician is often required to juggle priorities.

The interconnections between T2D and CHF are not simply via the association of T2D with vascular disease and hypertension. CHF is now known to be an insulin resistant state. This appreciation, coupled with the long-discussed disorder known as diabetic cardiomyopathy, implies that a positive feedback loop may exist. Regardless of the initiating event, T2D predisposes to CHF, and CHF may increase the risk of developing T2D. Evidence for a diabetic cardiomyopathy will be reviewed briefly, and a causal association between CHF and diabetes, here termed cardiogenic diabetes, will be reviewed. Finally, the implications of coexisting T2D and CHF for drug therapy will be considered very briefly. Throughout, CHF refers to systolic LV dysfunction. Diabetes (or T2D) refers to the common form of type 2 diabetes. A number of physiologically important events such as chronic inflammation, abnormal mitochondrial function in skeletal muscle, myocardial fibrosis, and myocardial apoptosis are beyond the scope, as are many important clinical issues such as concomitant renal or coronary disease, lipid abnormalities, hypertension, and others.

DIABETIC CARDIOMYOPATHY

A clinically relevant, direct effect of T2D on systolic function has been postulated for at least 30 years. The topic has been reviewed extensively [1,2]. Diabetic cardiomyopathy refers to myocardial dysfunction in the absence of prior myocardial infarction, coronary disease, valvular heart disease, hypertension or any other known cause of systolic dysfunction. Evidence that this disorder is a distinct clinical entity exists falls into four categories: longitudinal population studies, evaluation of patients with overt CHF, noninvasive evaluations of LV function among patients with diabetes but without known LV dysfunction, and animal studies.

Evidence for a Distinct Clinical Entity

One of the earliest suggestions that diabetes could directly cause CHF was reported by Rubler and colleagues in 1972 [3]. In this post-mortem study of patients with long-standing renal disease, it was noted that 4 patients had severe congestive heart failure. The authors suggested they had observed a "new type of cardiomyopathy...," and further postulated that "the myocardial disease seen in these cases is probably secondary to diabetic microangiopathy although the direct effects of the abnormal myocardial metabolism in diabetes could not be excluded." In 1974 the Framingham investigators reported on the incidence of new-onset CHF among patients with DM [4]. Among more than 5,000 subjects followed for 18 years, diabetes increased the risk of CHF by 2 to 5 fold, depending on the subgroup. This estimate of increased risk is widely cited, although current methods to assess associated coronary disease were of course not available. This influential report concluded "This excessive risk appears to be caused by factors other than accelerated atherogenesis and coronary heart disease. . . . Some form of cardiomyopathy is associated with diabetes, as a result of either small vessel disease or metabolic disorders." Other case studies similarly suggested a cardiomyopathy due to diabetes [5, 6]. More recently, Bertoni and colleagues [7] reported that among patients discharged with a diagnosis of cardiomyopathy, 0.76% of hospital discharges in the US, the prevalence of DM is about 1.5 times greater than in control.

A second line of evidence in favor of diabetic cardiomyopathy as a distinct entity arises from noninvasive evaluation of left ventricular function in patients with diabetes but without known heart disease. A general finding is that many patients with normal LV function at rest will develop abnormal function during dobutamine stress or during exercise [8, 9, 10, 11]. For example, among patients with type 1 diabetes, stroke volume during exercise is reduced. This observation has been replicated by other groups, but not all studies confirm the finding. For example, Nugent did not find impaired exercise response in patients with diabetes [12]. Borow and colleagues confirmed that some patients with diabetes have impaired exercise-induced increase in ejection fraction, but all patients with diabetes had normal contractile reserve as assessed with dobutamine challenge [13]. Studies of diastolic function tend to be more consistent and diastolic inflow patterns are often abnormal. For example, among well controlled patients with type 2 diabetes and no evidence of CHF, LV diastolic dysfunction was present in 60% of subjects [14].

A third category demonstrating a strong link between T2D and CHF is the simple observation that diabetes is highly prevalent among the large randomized trials of CHF. Of 13 trials reporting both the prevalence of diabetes and the measured ejection fraction, the total number of patients was 32,833. The weighted average EF was 28% and the prevalence of diabetes was 24%. It is important to point out that many patients with co-existing diabetes and CHF were likely excluded because the trials restricted enrollment of the elderly, patients with renal disease and patients with peripheral or cerebrovascular disease. There are obvious reasons for a close association of diabetes with heart failure, such as the prevalence of hypertension among patients with diabetes, the increased prevalence of coronary disease due to diabetes and associated dyslipidemias, and the poorer outcome after myocardial infarction. In general, these large trials did not distinguish ischemic and nonischemic etiologies. This may be important because diabetes conceivably exerts its adverse effect via progression of coronary disease. This hypothesis implies that diabetes, when associated with a dilated cardiomyopathy, would not have an adverse prognosis. However, if diabetes is driving the development of a dilated cardiomyopathy, then there should be an adverse effect. In the SOLVD trial [15] the presence of diabetes had no

significant effect on survival of patients without coronary disease. In the BEST trial, Domanski and colleagues found that diabetes was associated with increased mortality in patients with CHF due to coronary disease, but not in those diabetic patients with a nonischemic etiology [16].

Animal studies also provide some insight since many nutritional, genetic and behavioral variables can be controlled. In general, subtle or mild LV dysfunction is a consistent finding, and, like humans, diastolic dysfunction appears to be the most consistent finding [17, 18].

In summary, clinical, population and animal studies provide reasonable evidence that reduced insulin action in the myocardium, either due to myocardial insulin resistance or reduced circulating insuln, is associated with detectable impairment of left ventricular systolic function. However, the magnitude of the effect attributable solely to diabetes appears modest, and overt CHF due exclusively to diabetes is distinctly unusual. In large trials, admittedly with other objectives, diabetes does not appear to drive a poorer outcome among patients with a nonischemic cause for congestive heart failure, although prognosis is generally poor regardless of cause. Finally, in spite of an enormous population of patients with T2D, we simply don't see a corresponding number of patients with pure dilated cardiomyopathy. It seems reasonable to conclude that T2D renders the myocardium more susceptible to injury of any sort, and that T2D itself may directly cause minor abnormalities of LV function.

Proposed Mechanisms of Diabetic Cardiomyopathy

Diabetic cardiomyopathy has been attributed generally to altered substrate metabolism and to microvascular disease. A very early observation by Blumenthal in 1960 found that hyaline thickening was present in 50% of the autopsied patients with diabetes, but only 21% of the patients without diabetes [19]. Later, Factor et al. [20] reported capillary basement membrane thickening among patients with diabetes and normal or mildly depressed LV systolic function. Capillary basilar laminar thickening was also reported in humans by Fischer [21]. In diabetic rats, focal constrictions, microaneurysm formation and "microvascular spasm" were common [22]. In spite of these observations, there is also substantial evidence against a diabetic microangiopathy of the heart. First, in a study of humans with diabetes and perfusion fixation of the cardiac vessels, Sunni found no difference in small vessel disease or arterial structure among patients with diabetes compared to controls [23]. In an endomyocardial biopsy study, Sutherland did not detect any increase in cardiac capillary basal lamina thickness among diabetics [24].

Thus, evidence for cardiac microvascular abnormalities among patients with T2D is not compelling. Recent studies have directed attention to abnormalities of coronary flow reserve. Although there are limitations, the concept of coronary flow reserve is simple and important. Myocardial perfusion must increase in response to increased demand. Coronary flow in a normal human can increase 3 – 5 fold in response to either a physiological stimulus or pharmacological coronary vasodilation. If coronary flow does not increase normally in response to pharmacological challenge, presumably flow is limited either by epicardial or microvascular structural disease, or by impaired vasodilatory capacity. In principle, severely impaired coronary flow reserve could cause myocardial ischemia during ordinary fluctuations in myocardial oxygen demand. Multiple studies indicate impaired reserve among patients with diabetes. For example, Nitenberg reported impaired coronary flow reserve among patients with diabetes and without epicardial coronary disease [25]. Strauer found that maximal coronary flow and coronary flow reserve was impaired among diabetics, a finding confirmed by Pitkanen [26, 27].

Abnormal substrate metabolism and impaired insulin sensitivity have also been postulated. The normal myocardium responds to insulin by increasing glucose uptake and oxidation. Although most energy production in the normoxic heart is derived from fatty acid oxidation, described in more detail below, there is some suggestion that a small rate of glucose metabolism is necessary for normal function. Two metabolic concepts are supportive. First, oxidation of glucose to pyruvate produces ATP in the cytosol, whereas oxidation of long chain fatty acids eventually yields ATP at the outer surface of the mitochondria. There is some evidence that ATP produced in glycolysis is preferentially delivered to membrane-bound ion pumps; ATP from the mitochondria is delivered preferentially to the contractile apparatus. Therefore, the normal heart must be able to metabolize a small amount of glucose, independent of the actual ATP yield. Second, the heart must regenerate citric acid cycle intermediates continuously. Fatty acids yield only acetyl-CoA, but glucose metabolism provides pyruvate, a substrate for pyruvate carboxylase. The product, oxaloacetate, increases the concentration of citric acid cycle intermediates. A third effect of glucose oxidation, improved myocardial efficiency, is discussed below.

Finally, Roger Unger and colleagues [28] suggested that left ventricular dysfunction in an animal model of diabetes is caused by excess myocardial triglycerides, and that therapy with troglitazone reduced myocardial triglycerides with a concomitant prevention of LV dysfuction.

CARDIOGENIC DIABETES

Since the early 1990s, evidence has emerged that CHF predisposes to insulin resistance and T2D [29, 30]. CHF is associated with increased plasma catecholamines, and excess catecholamines impair insulin sensitivity. Paolisso and colleagues, therefore, reasoned that CHF may cause insulin resistance. In 1991 this group reported that nondiabetic euglycemic patients with congestive heart failure had increased plasma insulin, increased plasma fatty acids and impaired sensitivity to infused insulin. They suggested that chronic congestive heart failure may induce an insulin-resistant state secondary to an increase in plasma norepinephrine levels [31]. Amato et al. also found that CHF predicted T2D in elderly subjects [32]. Later, Swan and colleagues confirmed similar impairment in insulin sensitivity among patients with heart failure [33, 34].

Suskin et al. examined the prevalence of glucose and insulin abnormalities among patients with heart failure and stratified observations by NYHA functional class. By definition, all patients were euglycemic, but patients in NYHA FC III – IV had approximately twice plasma insulin compared to patients in FC I – II at equal fasting glucose [35]. Among patients with CHF due to valvular heart disease selected for the absence of diabetes and the absence of coronary disease, insulin resistant patients had lower ejection fractions, higher plasma free fatty acids (FFAs) and higher mortality rate [36]. Most recently, Doehner showed a stepwise decrement in insulin sensitivity across NYHA functional classes of heart failure [37].

If CHF causes insulin resistance, then what is the rate of development of T2D? In the Studies of Left Ventricular Dysfunction (SOLVD), among patients without diabetes at enrollment, new onset diabetes was detected in 22% of patients during follow-up [38], so it appears that the presence of heart failure may be predictive of diabetes. Myocardial injury, regardless of its origin, causes activation of the sympathetic and renin-angiotensin systems, so the potential effects of activation of each system on glucose metabolism will be considered.

Activation of the Sympathetic Nervous System

The myocardium must be able to alter heart rate and contractility virtually instantaneously. Presumably the rich sympathetic innervation allows the myocardium to quickly modulate cardiac output on a moment-to-moment basis as needed by the peripheral organs for normal function. It is now appreciated that chronic activation of the sympathetic nervous system occurs during congestive heart failure. While beneficial in the sense of providing short-term improvement in contractility and blood pressure, the body may become insulin resistant and therefore susceptible to T2D.

Activation of the SNS has diverse effects on metabolism; only three points are briefly summarized here. First, splanchnic and skeletal vasoconstriction mediated by alpha adrenergic vascular receptors shunts both insulin and glucose away from skeletal muscle and other organs. Removal of a glucose load from the circulation is largely due to skeletal muscle glucose uptake. At least in principle, vasoconstriction should reduce glucose utilization and clearance, and in fact, alpha adrenergic blockers improve insulin sensitivity [39]. Second, the sympathetic nervous system increase lipolysis and is associated with elevated plasma free fatty acids. In normal human subjects, infusion of norepinephrine increase plasma FFAs, and elevated FFAs are a feature of CHF. Elevated FFAs, in turn, may have multiple effects including inhibiting insulin - stimulated glucose clearance, indirect inhibiting pyruvate dehydrogenase (an enzyme critical for glucose oxidation), and stimulating hepatic glucose production. The so-called "porto-visceral hypothesis" suggests that diabetes is due to excess visceral lipolysis and release of FFAs directly to the liver via the portal circulation where they may be stored (resulting in fatty liver), stimulate glucose production and reduce sensitivity of the liver to insulin, thus further driving glucose production. Although their relative importance is unknown, each of these effects of FFA predispose to insulin resistance. Third, excess FFAs may be deposited as triglycerides in skeletal muscle, a recently-proposed mechanism for skeletal insulin resistance. In summary, increased plasma free fatty acids may in principle have multiple adverse effects on glucose tolerance. Finally, circulating FFAs may also impact the pancreas since high concentrations of FFAs are toxic to beta cells and may contribute to the progressive decline in beta cell mass. It is tempting to speculate that some patients with CHF may be particularly susceptible to the diabetogenic effects of SNS overactivity.

Activation of the Renin-Angiotensin-Aldosterone System

An early consequence of CHF is disruption of systemic fluid, electrolyte and blood pressure regulation. Consequently, the renin-angiotensin-aldosterone system, a cluster of hormones that coordinate renal, adrenal and peripheral vascular function, is activated by CHF. Inhibition of the system at various levels now plays a key role in current cardiovascular pharmacology. A great deal of emphasis, beginning about 15 years ago, was placed on treating patients with both hypertension and diabetes with an ACE inhibitor for the purpose of renal protection. More recently, a number of studies have consistently found that ACE inhibition reduces the risk of diabetes itself among patients at high risk for diabetes. Other evidence that ACE inhibition improves insulin sensitivity has generated strong interest in the role of the RAA system as a causative factor in T2D.

The clinical evidence that activation of the RAA system plays a role in developing diabetes is reasonably strong. In the Studies of Left ventricular dysfunction, SOLVD, a marked reduction of new diabetes was observed among those patients treated with enalapril. At about 3 years of

follow up, more than 22% in the placebo group had developed diabetes, compared to 5.9% in the enalapril treated group ($p < 0.0001$). In a trial of candesartan, an ARB, in CHF, patients were randomly assigned to up-titration on candesartan or placebo. The results were not as dramatic, but the risk of diabetes was also reduced (6% on candesartan vs. 7% on placebo; hazard ratio 0.78, CI 0.64 - 0.96, $p=0.02$).

Several prospective randomized trials examined the cardiovascular protective effects of an ACEI (in these studies, either lisinopril, enalapril, captopril or ramipril) compared to placebo, or a thiazide, or a thiazide-beta blocker combination. Four of the prominent trials will be mentioned briefly. In the Heart Outcomes Prevention Evaluation (HOPE) patients at high risk for cardiovascular events were randomly assigned to ramipril or placebo [40]. Among these patients, the risk of developing new diabetes at a follow up of 4.5 years was about 3.6% in the ramipril group compared to 5.4% in the placebo group ($p<0.001$). In the Captopril Prevention Project (CAPP), captopril was compared to conventional therapy among patients with hypertension. Thus, unlike the HOPE, the comparison was not to placebo [41]. The risk of diabetes was lower in the captopril group compared to the conventional therapy group ($p < 0.03$) but it is not clear if this is a beneficial effect of captopril or an increase in the risk of diabetes due to thiazide diuretics and beta blockers. A third trial of interest was the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). In this trial [42] patients were assigned to a calcium channel blocker, amlodipine, an ACE inhibitor, lisinopril, or a thiazide, chlorathalidone. The risk of diabetes was 9.6% in the chlorthalidone group, 7.4% in the amlodipine group, and 5.8% in the lisinopril group ($p<0.001$ lisinopril vs. chlorthalidone). There was no effect on total mortality or fatal heart disease or nonfatal myocardial infarction among these groups. In the Swedish Trial in Old Patients with Hypertension-2, patients > 70 were randomized to a thiazide, a beta blocker or an acei. There was no difference in either the efficacy of blood pressure control nor the primary endpoint of fatal stroke, fatal myocardial infarction or other fatal cardiovascular event[43]. Regardless of the treatment group, the risk of diabetes was about the same, 10%, in this elderly population. In summary, three of four large trials of ACE inhibitors among patients with hypertension or other risk factors for cardiovascular disease suggest about 15 - 30% reduction in the risk of developing diabetes compared with thiazides, calcium channel blockers or beta blockers. The one trial did not show this effect involved substantially older patients.

These studies have provoked intense interest in whether ACE inhibition improves sensitivity to insulin. Interestingly, in light of the above clinical studies of the effect of RAS inhibition on development of diabetes, the effects of relatively acute RAS inhibition on glucose metabolism is unclear in some respects. It is generally agreed that ACE inhibition does not impair glucose metabolism or predispose to diabetes, in contrast to beta blockers and numerous reports of adverse effects of diuretics. Many of the studies evaluating the effects of ACE inhibition on glucose metabolism examined insulin-mediated glucose disposal among patients with hypertension. Among the published studies about half showed an increase in insulin sensitivity attributable to ACE inhibition, but the other studies showed no effect.

DOES CHF CAUSE CARDIAC INSULIN RESISTANCE AND CARDIAC DIABETES?

The previous section described some evidence and a physiological rationale for whole-body insulin resistance secondary to CHF. The development of insulin resistance in the myocar-

dium, as a consequence of CHF could be termed "cardiac diabetes." With this perspective, the absence of overt systemic T2D does not preclude adverse cardiac effects due to insulin resistance.

The possibility that cardiac insulin resistance is a feature of heart failure may be therapeutically relevant. Blocking the consequences of neurohumoral activation in heart failure has proven to be a remarkably successful model for high-impact clinical advances over the past 25 years. Nevertheless, patients with CHF experience continued high morbidity and mortality. More recent trials with endothelin-l receptor blockers and cytokine antibodies [44, 45] were disappointing and suggest that alternative options may be important. Perhaps one clue arises from a broad reclassification of drugs for CHF into one of three groups: drugs that are likely to chronically increase myocardial oxygen demand, drugs that have neutral effects on myocardial oxygen demand at clinical levels, and drugs or combinations that are likely to reduce myocardial oxygen demand. With this classification, the implications are obvious: new pharmacological methods to improve mortality should focus on an old idea: reduce myocardial oxygen demand and improve cardiac energetics.

Myocardial Substrate Preference

The normal heart possesses the enzymatic machinery to oxidize every relevant class of substrate at a high rate. The plasma concentration of long chain fatty acids, short chain fatty acids, odd carbon fatty acids, lactate, pyruvate, ketones and glucose vary over an enormous range depending on acute and chronic changes in nutritional state, exercise, and coexisting diseases. For example, plasma glucose spikes after a meal, low carbohydrate diets cause marked ketosis, lactate concentrations increase 10-fold with extreme exercise, etc. Unlike the brain, the heart has the capacity to switch rapidly among substrates for oxidation to provide high rates of continuous ATP generation. The "choice" of substrates simply depends on neurohumoral conditions and available substrates.

This metabolic flexibility of course is advantageous under most conditions. However, there are subtle consequences of switching among substrates. Every college biochemistry book describes the yield of ATP after complete oxidation of glucose compared to a long chain fatty acid, palmitate. ATP yield is far greater per molecule of palmitate oxidized compared to glucose, largely because one mole of palmitate yields 8 moles of acetyl-CoA compared to only 2 molecules of acetyl-CoA from one mole of glucose. In this sense, the energy yield from fatty acids is more "efficient" than from glucose. However, these same calculations may be used to determine the yield of ATP per mole of oxygen consumed. With this definition of efficiency, glucose is a better substrate since its oxidation yields about 12-15% more ATP per mole of oxygen consumed.

Is this distinction physiologically relevant? The normal heart is obtaining 60 - 70% of its energy from fatty acids and the balance from a mix of lactate, pyruvate and ketones. All of these fluctuate in concentration and all are subject to metabolic control mechanisms, some overlapping. So it is highly implausible that a heart is ever oxidizing 100% long chain fatty acids or that any intervention could shift the heart to 100% glucose oxidation. Therefore, any shift in substrate oxidation will produce a minor, at best, change in myocardial efficiency. In the normal heart, this difference is irrelevant to myocardial function, since myocardial oxygen delivery is not limiting.

However, in the failing heart, the substrate selection may be important because there is evidence that the failing heart is relatively oxygen limited. More than any other organ in the body, the heart is required to generate ATP continuously at a high rate and to change the rate of ATP

production in response to peripheral demands. The heart, even including the energy buffering provided by the phosphocreatine system, has virtually no energy reserve *compared to the overall demand.* Therefore, it is plausible that a quantitatively small increase in the steady state rate of ATP production perhaps achieved by shift in substrate utilization could prove beneficial to a patient.

DRUG THERAPY FOR PATIENTS WITH COEXISTING CHF AND T2D

Metformin, insulin, and thizolidinediones are widely used for the management of T2D, yet may have adverse effects among patients with CHF. Similarly, beta adrenergic blockers and diuretics, essential drugs in the management of CHF, have long been known to reduce insulin sensitivity and to increase the risk of diabetes. Management of these patients is further complicated by the fact that many patients with T2D have elevated creatinine, making therapy with ACE inhibitors more problematical. The practicing internist is therefore required to make difficult judgments about whether a drug with known mortality or other benefits can be justified among patients with coexisting T2D and CHF.

Metformin

Metformin is widely used, effective and well-tolerated by most patients with T2D. It is the only therapy for hyperglycemia known to reduce macrovascular complications among patients with T2D. It reduces hepatic gluconeogenesis, a key feature of the hyperglycemia of T2D [46]. Another group of agents, the thiazolidinediones (TZDs), are associated with weight gain and volume expansion, as is insulin. Unlike both, metformin is not associated with weight gain. Thus, metformin is an important and perhaps optimal drug for many patients with T2D. However, metformin is chemically related to phenformin, a hypoglycemic agent associated with lactic acidosis, particularly in renal disease and in the setting of hemodynamic compromise. An influential letter [47] suggested that patients with CHF are at high risk for profound lactic acidosis, and the package insert was eventually revised to essentially exclude all patients with CHF. In view of the known physiology of CHF – impaired renal perfusion, risk of hypotension – the decision is reasonable. However, a number of recent reports suggest that metformin may be relatively safe [48]. Eurich et al found that among patients with CHF, fewer deaths occurred in the metformin group compared to the sulfonylurea group [49]. In Medicare recipients, Masoudi et al. [50] found that either metformin or a TZD improved survivial among patients with CHF, and metformin-treated patients were hospitalized less frequently.

These retrospective database studies do not allow firm conclusions. It is conceivable that the good outcomes observed in these patients were simply a consequence of clinical vigilance coupled with careful selection of patients with good renal function and mild CHF. Others have suggested that the current recommendations prevent the use of a valuable agent in patients with both T2D and CHF, and that the prescribing guidelines should be reconsidered [51, 52]. Until that point, however, all clinicians must be aware that metformin is not indicated among patients with CHF.

Thiazolidinediones

Thiazolidinediones improve sensitivity to insulin and thereby improve glucose control. These drugs are agonists of peroxisome proliferator–activated receptor-gamma nuclear receptors.

Activation of this PPAR causes diverse effects resulting in increased glucose disposal, and the TZDs have beneficial effects of risk factors for cardiovascular diseases. In the landmark U.K. Prospective Diabetes Study, progressive deterioration of glucose control was demonstrated despite intensive therapy. The deterioration in blood glucose control is likely to be due to a steady reduction in beta cell mass or function. Therefore, sensitizing the periphery to insulin is a logical therapeutic goal. Furthermore, TZDs may also improve beta cell function and increase insulin secretion, and may preserve beta cell mass.

TZDs also increase plasma volume by 2 - 5% resulting in peripheral edema, and symptoms of CHF may be exacerbated in patients with severe LV dysfunction. There are multiple case reports of patients developing progressive symptoms and physical findings of heart failure. Fortunately, these patients responded to discontinuation of the TZD and diuretic therapy. Thiazolidinedione therapy is probably inappropriate in patients with NYHA functional class III or IV heart failure.

Insulin

Diabetes may eventually lead to treatment with insulin. The advantage of insulin is that it is effective and relatively inexpensive for control of plasma glucose, but it is not preferred by patients compared to oral medications. It is also associated with weight gain. Theoretically, if insulin is likely to provoke hypoglycemia, this could lead to sympathetic activation and dysrhythmias among patients with heart failure. Recently, poorer outcomes have been associated with insulin therapy among patients with diabetes and heart failure but it is not known if insulin is a marker for advanced disease or if insulin itself has adverse effects [53].

Diuretics

Symptom reduction is essential for CHF therapy. However, many diuretics have been implicated in the development of T2D, particularly thiazides. Presumably the mechanism is depletion of body potassium and desensitization of the pancreas to glucose stimulated insulin secretion. For practical purposes, there is no alternative to diuretics for patients with CHF. The only protection is adequate potassium repletion, close monitoring of plasma potassium, and use of the minimum dose of the diuretic adequate to control edema.

Angiotensin-Converting Enzyme Inhibitors

Angiotensin-converting enzyme inhibitors reduce mortality in CHF and reduce renal complications in patients with established diabetes. Somewhat unexpectedly, angiotensin-converting enzyme inhibitors also improve glucose metabolism, discussed above. If a person is intolerant of ACEIs, an angiotensin II blockers may be substituted, although they may not have equal mortality benefit. It is not known if combined ACEI and ARB therapy can improve outcome among patients with both CHF and diabetes. Hypotension, hyperkalemia and progressive renal insufficiency are well-known risks of ACEIs. These risks are more pronounced among patients with both diabetes and CHF, especially in preexisting renal insufficiency and with associated nonsteroidal pain medications. Nevertheless, among patients with CHF the benefits of interrupting activation of the RAA system are overwhelming. For this reason every effort including

initiation of an ACE inhibitor at a low dose and gradual upward titration should be made even among patients with mildly elevated creatinine.

β-Adrenergic Blockers

Beta-blockers inhibit the hyperactive sympathetic nervous system. Among patients with CHF, these agents increase myocardial contractility and reduce mortality. A long standing concern associated with beta blocker therapy is the possibility of increased risk of diabetes. Gress et al. examined the risk of developing diabetes among 12,550 adults, 45-64 years old, who did not have diabetes at enrollment [54]. New cases of diabetes at 6 years were analyzed with respect to drug therapy. After adjusting for age and numerous risk factors for diabetes, patients taking beta blockers were at increased risk of developing diabetes. Interestingly, calcium channel blockers, thiazides, and ACE inhibitors did not confer excess risk.

This reported excess risk of 28% for developing diabetes should be balanced against two factors. First, this report did not distinguish first, second and third generation beta blockers. In particular, carvedilol has alpha blocking properties and does not appear to have the same adverse effects on glycemic control, and may be superior to either metoprolol or atenolol in this respect. Second, beta blockers have undoubted mortality benefits among patients with heart failure. Of course, the adverse hemodynamic effects such as fatigue, bradycardia and volume retention must be considered, but there must be strong reasons not to use a beta blocker in a patient with CHF.

Aldosterone Inhibitors

Spirononlactone and eplerenone are aldosterone inhibitors, and are typically classified as diuretics. These agents reduce all-cause mortality among patients with severe CHF through a mechanism that is not simple diuresis but probably beneficial effects on fibrosis and LV remodeling. The relevant complication, hyperkalemia, is related to their renal effects. Patients with diabetes, especially with renal insufficiency, are more likely to develop hyperkalemia due to aldosterone blockade. The danger, of course, is increased among patients taking potassium supplements or in the setting of volume depletion due to excess diuresis, vomiting or diarrhea. The key is patient education and close surveillance.

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