

Adaptation and Maladaptation of the Heart in Diabetes: Part I General Concepts

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Diabetes mellitus (type 2 diabetes) is as much a disease of modern lifestyle as it is a disease of genetic predisposition. Worldwide, there are about 143 million patients with diabetes, almost 5 times more than estimates of 10 years ago.^{1,2} Heart disease, often presenting as cardiomyopathy, is the leading cause of death among patients with diabetes mellitus (Figure 1).³ Like diabetes, the prevalence of heart failure also continues to rise in Western countries.⁴ Diabetes, in turn, is the largest comorbidity of patients with heart failure and adversely affects outcomes of cardiovascular disease.⁵ The trend is unmistakable; both insulin resistance and heart failure have emerged as major worldwide epidemics. It is therefore timely to take a fresh look at the effects of diabetes on the heart.

The difficulties in making a causal connection between diabetes and heart failure are formidable. Some simple definitions remain elusive. For example, the distinction between the insulin-deficient (type 1) and insulin-resistant (type 2) forms of diabetes on the one hand, and the distinction between systolic and diastolic dysfunction as causes of heart failure, on the other hand, are hard to define. The known trophic and hemodynamic effects of insulin in healthy individuals,⁶ the well-described endothelial dysfunction, the deposition of advanced glycation end products, and an accelerated progression of atherosclerosis in patients with diabetes add further complexities to the clinical picture of heart failure in diabetes. Nonetheless, diabetes as a primary cause for heart failure was already recognized more than a century ago, when heart failure was regarded a “frequent and noteworthy complication of diabetes mellitus,”⁷ and physicians proposed already then that “heart disease in diabetes can be traced to an abnormality in metabolism.”⁸

Hyperglycemia and hyperinsulinemia increase the risk of fatal cardiovascular disease in the form of premature and accelerated coronary artery disease.^{9–11} The increased prevalence of coronary artery disease in diabetes is associated with a constellation of risk factors that has long been appreciated.^{12,13} We have speculated that insulin resistance and coronary artery disease may have a common root.¹⁴

Patients with type 2 diabetes are frequently obese, and often suffer from hypertension and exhibit dyslipidemia (high serum triglyceride and high VLDL and LDL, as well as low HDL cholesterol levels).⁹ Because angina is not always a reliable index of ischemia in patients with coronary artery disease,^{15,16} ischemia often goes undetected and contributes significantly to heart failure.

A number of clinical and experimental studies suggest that diabetes results in functional, biochemical, and morphological abnormalities independent of myocardial ischemia. Early studies on substrate metabolism of the human heart have revealed that glucose uptake is decreased, whereas fatty acid uptake is increased by the heart of patients with diabetes.¹⁷ In light of an abundance of substrate supply in the blood and impaired contractile function of the myocardium, it is appropriate to ask the question, “Why does the heart fail in the midst of plenty?” In the first part of our review, we will discuss the effects of diabetes on energy substrate metabolism and contractile function of the heart. In the second part, we will focus on potential molecular mechanisms by which energy substrate metabolism and gene expression interact during adaptation and maladaptation of the heart to diabetes.

Functional Adaptation and Maladaptation of the Heart in Diabetes

Longitudinal studies show that patients with diabetes demonstrate a substantially increased lifetime risk of congestive heart failure (CHF),¹⁸ and that diabetics are over-represented in large CHF databases.¹⁹ The question of whether there is a diabetes-specific cardiomyopathy has been debated for decades and is not yet answered.^{19–21} Circumstantial evidence for a diabetic cardiomyopathy in humans rests on a number of morphological, functional, and biological observations.

First, patients with diabetes exhibit changes in cardiac structure and cardiomyocyte ultrastructure that can plausibly be attributed to the diabetic milieu. On the macroscopic level, echocardiographic screening of large databases has demonstrated that diabetes is associated with concentric left ventric-

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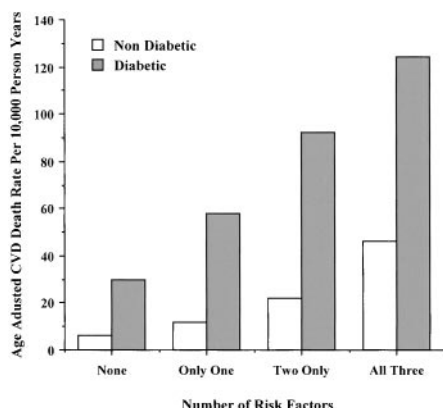


Figure 1. Multiple Risk Factor Intervention Trial (MRFIT). Age-adjusted cardiovascular disease death rates (per 10 000 person-years) by presence of number of risk factors in men with and without diabetes. Reproduced with permission from Stamler et al.³ Copyright 1993 American Diabetes Association (*Diabetes Care*. 1993;16:434–444). Reprinted with permission from the American Diabetes Association.

ular hypertrophy and increased heart mass, with mildly reduced left ventricular systolic performance.²² On the microscopic level, histological studies of autopsy and biopsy specimens demonstrate that diabetic humans and animals made diabetic share a constellation of cardiac morphological abnormalities, including myocyte hypertrophy, perivascular fibrosis, and increased quantities of matrix collagen, cellular triglyceride, and cell membrane lipid. All of these findings are consistent with the nonenzymatic glycation of vascular and membrane proteins, increased cellular fatty acid uptake, and hyperglycemia-induced oxidative stress, which are characteristic of the diabetes state.^{23,24}

These morphological changes, especially when considered together with the changes in myocardial calcium metabolism and contractile protein composition observed in experimental diabetes, would be predicted to confer clinically significant impairment in diastolic compliance. Doppler echocardiographic studies have revealed that qualitatively similar patterns of diastolic dysfunction are an early feature of diabetes in both animal models²⁵ and humans.^{26,27} In patients with diabetes, the reduction of diastolic compliance is associated with characteristically abnormal myocardial acoustic properties and correlates positively with the severity and duration of diabetes and negatively with the ability to perform treadmill exercise.²⁸ The relevance of this type of diastolic dysfunction to diabetes per se is clouded by the frequent coexistence of hypertension with diabetes; however, the recognition that impaired left ventricular diastolic filling can be demonstrated very early in the course of monogenetic type-2 diabetes in animal models, before the onset of hypertension, vasculopathy, or even fasting hyperglycemia, suggests diastolic dysfunction is an effect of diabetes itself.²⁵ An association of diabetes with myocardial diastolic dysfunction and poor exercise performance is undisputed.

There is less evidence that diabetes itself can cause left ventricular dilatation and failure in the absence of coronary artery disease or hypertension. Nevertheless, because of the coexistence of diabetes, hypertension, and coronary artery

disease, these factors may act synergistically to produce heart failure on the basis of left ventricular systolic dysfunction. For this reason, it is difficult to target a diabetes-specific metabolic, functional, or structural abnormality for pharmacological treatment of heart failure in diabetes. Furthermore, it still remains to be seen whether the degree of metabolic control affects the function of the heart in diabetes. The focus therefore shifts once more to the identification and treatment of comorbidities in diabetes.

Comorbidities in Diabetes

The synergy between coronary artery disease and diabetes is clearly demonstrated by observations from the large number of diabetic patients who have been enrolled in thrombolytic trials. Relative to non-diabetics, patients with diabetes demonstrate impaired recruitment of contractile reserve in non-infarct segments,^{29,30} greater reduction in global left ventricular function,³¹ and greater incidence of CHF^{32,33} after an acute myocardial infarction.

Synergy between diabetes and hypertension may be an even more important issue. The 2 conditions are associated with qualitatively similar changes in cardiac ultrastructure, gene expression, and diastolic function, and evidence from both animal³⁴ and human^{35,36} studies suggest that their effects are independent and synergistic. At the cellular level, both diabetes and hypertension have been associated with an induction of cardiomyocyte apoptosis and necrosis in the human heart mediated by oxidative stress resulting from local production of angiotensin-II by the cardiac renin-angiotensin system (RAS).³⁶ Because hypertension activates both cardiac and systemic RAS, whereas hyperglycemia promotes the formation of reactive oxygen species (ROS) as a reaction product of protein glycation, hypertension and diabetes might synergistically promote apoptotic cardiomyocyte loss. In patients with diabetes, the development of hypertension can then be expected to initiate the transition from compensated/hypertrophied to decompensated/dilated cardiomyopathy. This hypothesis is supported by recent clinical trials demonstrating that tight blood pressure control dramatically reduces the incidence of heart failure and cardiovascular mortality in patients with established diabetes.^{37,38}

Lastly, one of the most important comorbidities is diabetic nephropathy, which shares certain features with small vessel disease in the retina.³⁹ A discussion of this topic would be beyond the scope of this review.

Substrate Selection and Insulin Action in Heart and Skeletal Muscle

Diabetes is first and foremost a disorder of abnormal insulin secretion and/or impaired insulin action. Approximately 10% of adults with diabetes mellitus exhibit absolute insulin deficiency (insulin-dependent, type-1 diabetes), and the remainder suffer from varying degrees of target-tissue insulin resistance (non-insulin-dependent [NIDDM], type-2 diabetes).⁴⁰ Other than the heart, the main target tissues for insulin's metabolic actions are the liver, skeletal muscle, and adipose tissue. Of these, skeletal muscle is the major quantitative glucose sink, accounting for 70% of the disposal of an administered glucose load under most conditions.⁴¹ From the

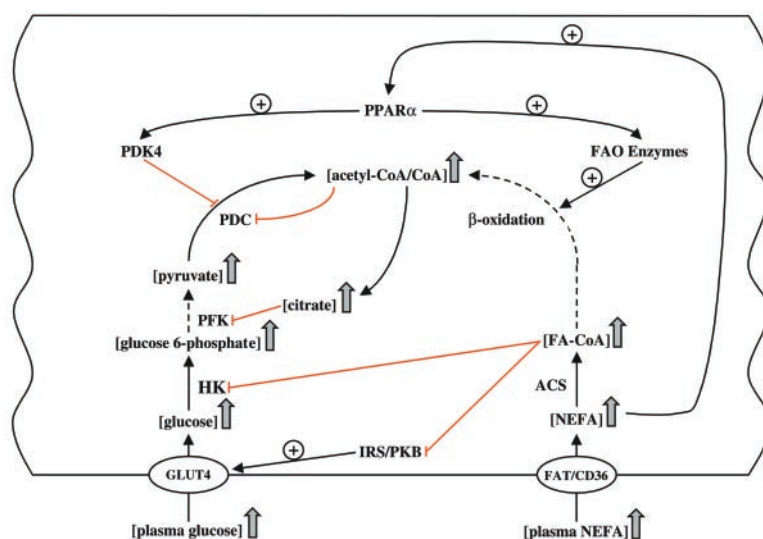


Figure 2. Mechanisms of fatty acid inhibition on glucose utilization by the heart. During diabetes, both plasma glucose and plasma nonesterified fatty acid (NEFA) levels are elevated. The latter results in increased intracellular levels of fatty acids and their fatty acyl-CoA (FA-CoA) derivatives. FA-CoAs inhibit insulin mediated glucose transport by inhibiting insulin receptor substrates (IRS) and protein kinase B (PKB).^{54,68} FA-CoAs can directly inhibit hexokinase (HK).⁹⁷ Increased β -oxidation (due to increased substrate availability and increased gene expression of fatty acid oxidation [FAO] enzymes via peroxisome proliferator-activated receptor α [PPAR α] activation) results in an increase in the mitochondrial acetyl-CoA/CoA ratio. The combined effects of increased PDK4 expression (induced through fatty acid activation of PPAR α) and increased acetyl-CoA/CoA ratio severely inhibit the pyruvate dehydrogenase complex (PDC). In addition, the increased acetyl-CoA/CoA ratio promotes citrate efflux from the mitochondrion into the cytosol, where it is able to inhibit phosphofructokinase (PFK). Despite decreased insulin-mediated glucose transport, glucose uptake by the diabetic heart is comparable to the normal heart because of the hyperglycemia.⁷⁶ Glycolytic intermediates therefore

accumulate in the cardiomyocyte.⁹⁸

perspective of fuel homeostasis, the heart is only a minor site of whole body glucose disposal. Why, then, is the heart an insulin-sensitive organ at all? A brief review on energy substrate selection by the heart may provide an answer to this question.

Glucose uptake by muscle (cardiac and skeletal muscle) is determined primarily by 2 separate but interrelated factors, namely the local concentrations of insulin and the intensity of exercise/contraction. Furthermore, nonesterified fatty acids (NEFAs) modulate insulin-mediated glucose transport. Figure 2 integrates well-known and more recently described mechanisms by which fatty acids regulate glucose metabolism in the heart. Earlier, it was shown that fatty acids inhibit glucose oxidation to a greater extent than glycolysis, and glycolysis to a greater extent than glucose uptake by the heart.⁴² Later, we have shown the reverse is true as well; glucose suppresses the oxidation of long-chain fatty acids,⁴³ potentially through malonyl-CoA inhibition of carnitine palmitoyltransferase I.⁴⁴ These observations expose a complex and highly regulated interaction of substrates for provision of the optimal fuel for respiration in a given environment.

Insulin secretion into the bloodstream (or insulin administration) increases muscle glucose uptake by 2 major mechanisms. Insulin directly stimulates myocyte glucose uptake by increasing glucose transporter (GLUT) 4 translocation to the cell surface. In addition, insulin inhibits release of NEFA from adipose tissue, thus lowering plasma NEFA levels and therefore removing NEFA-mediated inhibition of glycolysis and pyruvate oxidation (as well as the inhibitory effect of NEFA on insulin signaling). The magnitude of glucose consumption observed at any particular insulin level in vivo will thus be reduced to the extent that other conditions (eg, fasting, catecholamine release, or heparin administration) concomitantly raise circulating NEFA levels. This principle of glucose-NEFA substrate competition is so striking that early investigators incorrectly assumed type 2 diabetes was

secondary to chronic elevation in plasma NEFA levels alone.⁴¹ The suppression of glucose oxidation by fatty acids, however, is only one component of a complex system of metabolic interactions.

Fatty acids undoubtedly impair insulin-mediated glucose disposal (Figure 2). High-fat feeding has repeatedly and consistently been shown to result in impaired glucose tolerance and decreased muscle insulin sensitivity.^{45–47} The exact mechanism by which fatty acids inhibit insulin action are not known, but recent studies suggest a role of various isoforms of protein kinase C (PKC), especially PKCs θ and ϵ .^{48–50} Discordance between the rates of fatty acid availability and/or uptake with that of fatty acid oxidation results in increased intracellular long chain fatty acyl-CoA concentrations. The latter, either directly or through increased generation of diacylglycerol (DAG), activates PKCs.⁴⁸ PKCs are serine/threonine kinases capable of causing the phosphorylation of the insulin receptor and/or the insulin receptor substrates, either directly or through activation of additional kinases (eg, MAP kinase), thereby preventing insulin-mediated tyrosine phosphorylation and impairing insulin action.^{51,52} Increased intramuscular fatty acids and increased PKC activity have been reported in insulin resistant skeletal muscle.^{49,50,53} Recent studies suggest that fatty acids also inhibit insulin signaling at the level of PKB, possibly via ceramide.⁵⁴ Taken together, normal insulin response is a prerequisite for balanced fuel provision to the heart.

Glycolysis and Substrate Competition

When substrate competition is examined in isolated perfused hearts, the following has been observed. During aerobic perfusion at normal workloads, the heart generates the energy required to perform work primarily by oxidizing NEFA with smaller contributions from glycolysis and oxidation of pyruvate and other substrates.⁴³ Both theoretical considerations and empiric observations in animal models suggest glycolysis and pyruvate oxidation become more important under condi-

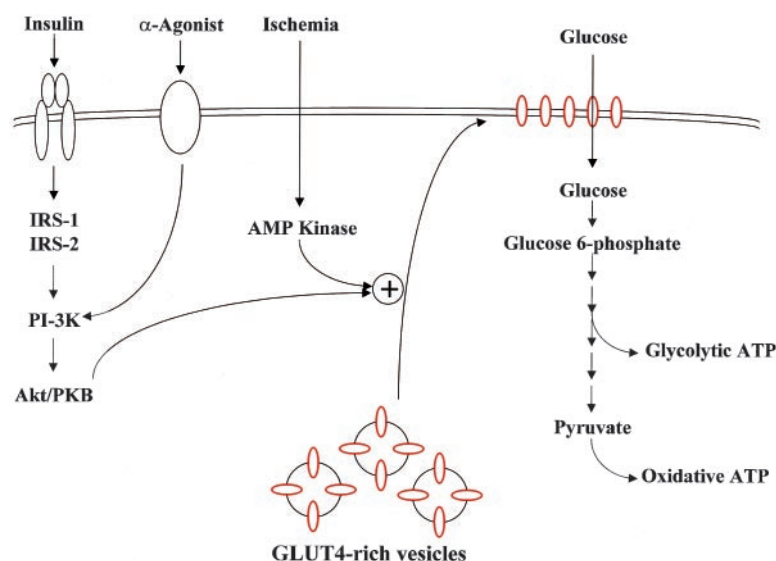


Figure 3. Hypothetical mechanisms of cardiac glucose transport and metabolism. The figure depicts the hypothetical mechanisms by which insulin, ischemia, and α -adrenergic stimulation promote glucose transport in the heart, as reported in previously published studies. The insulin and α -adrenergic pathways converge on phosphatidylinositol 3-kinase (PI-3K).⁵⁹ In contrast, evidence suggests a role for AMP-activated protein kinase (AMPK) in ischemia-induced glucose transport.⁶⁰ All 3 pathways induce the translocation of GLUT4-rich vesicles to the cell surface, resulting in increased glucose transport. ATP can be generated by either partial or full oxidation of intracellular glucose.

tions of energy supply-demand imbalance, including ischemia, hypoxia, and pressure overload.^{55–57}

The myocardial adaptation to energetic stress also includes recruitment of specific elements of the intrinsic cardiac insulin-response system. Insulin, ischemia, and stimulation of the α 1 adrenergic receptor induce sarcolemmal GLUT4 translocation by mechanisms operating through PI 3-kinase and AMP kinase, in rat^{58,59} and dog⁶⁰ heart (Figure 3). The potential importance of ischemic GLUT4 translocation is illustrated by the demonstration that cardiac-specific GLUT4 knockout impairs postischemic contractile recovery of the mouse heart under certain conditions.⁶¹

The oxidation of pyruvate is limited by the rate at which pyruvate is converted to acetyl-CoA by the pyruvate dehydrogenase complex (PDC) in mitochondria. Because glucose oxidation requires less oxygen per mole of ATP formed than NEFA oxidation, myocardial PDC activity correlates, not unexpectedly, with contractile performance in the postischemic heart. Here, both PDC activity and contractility are depressed in tandem at the onset of reperfusion after an episode of ischemia^{62,63} and administration of either pharmacological activators of PDC (eg, dichloroacetate),⁶⁴ or ranolazine,⁶⁵ or supplemental pyruvate⁶⁶ increases not only the relative contribution of glucose to the Krebs cycle substrate pool but also cardiac power.

Insulin Signaling and Insulin Resistance

The molecular targets of insulin action and pathways of insulin signaling have recently been reviewed,^{67,68} and are summarized as follows. Insulin receptor binding induces receptor auto-phosphorylation and initiates phosphorylation cascades involving various signaling molecules within the cell. Major gains in understanding the molecular basis of insulin action have followed identification of novel intracellular substrates for the insulin receptor tyrosine kinase. Regarding glucose metabolism, numerous lines of evidence suggest that the most important step in insulin signaling is translocation of the insulin-sensitive transport protein GLUT4 from an intracellular compartment to the sarcolem-

ma.⁶⁹ In the fasting state, only $\approx 15\%$ of total cardiomyocyte GLUT4 protein can be isolated from the sarcolemma, whereas this amount increases to $\approx 80\%$ within 30 minutes of insulin administration. Studies using specific inhibitors have revealed that the action of 4 protein kinases (phosphoinositol 3-kinase [PI 3-K], Akt/protein kinase B [PKB], and the atypical protein kinase C [aPKC] isoforms ζ and λ) are required for insulin-dependent sarcolemmal GLUT4 translocation.^{67,70,71} Although specific defects in the muscle insulin receptor, insulin receptor substrates, PI 3-K, PKB, or aPKC would seem logical candidates for the inherited nature of muscle insulin resistance, isolated defects in these individual elements in fact account for only sporadic cases of diabetes.⁷² In spite of this wealth of information, the specific defect in insulin-stimulated GLUT4 translocation, which conveys muscle insulin resistance, remains obscure. Identification of novel branches of the insulin-signaling cascade,⁷³ and how factors such as fatty acids interact with components involved in insulin-mediated glucose transport,⁶⁸ will undoubtedly shed light on the complex genetic-environment interactions involved in the development of insulin resistance.

Myocardial Metabolism in Diabetes

Alterations in myocardial metabolism are an early consequence of experimental diabetes in animals and had already been recognized by Starling and Evans⁷⁴ nearly a century ago. The early investigators made 2 important observations: glucose uptake and the respiratory quotient (RQ) both decrease in the heart of a diabetic animal, and the metabolic abnormalities persist when the heart from a diabetic animal is perfused ex vivo with blood from a non-diabetic animal. Despite these early observations, it took many decades to recognize that diabetes is as much a disease of dysregulated fatty acid metabolism as it is a disease of dysregulated glucose metabolism.⁷⁵ The normal reliance of the heart on fatty acid metabolism for energy production is increased in diabetes.⁷⁶

Because diabetes more than doubles the chance of developing congestive heart failure in patients with a variety of

cardiovascular diseases,^{32,33} it has been speculated that acute⁷⁷ and chronic metabolic alterations may impair the energetic and functional adaptation of the heart to ischemia or hemodynamic overload. For example, administering the islet toxin streptozotocin to rats produces insulin-deficient diabetes, reduces myocardial expression of GLUT4 and hexokinase,⁷⁸ induces fetal isoforms of sarcomeric proteins,⁷⁹ decreases sarcoendoplasmic reticulum Ca^{2+} -ATPase 2a transcript levels,⁷⁹ and reduces myocardial PDC activity.⁸⁰ Such hearts exhibit reduced rates of glycolysis and pyruvate oxidation, preceding depressed contractility; administering the PDC agonist dichloroacetate coordinately normalizes glucose oxidation and contractility.⁸⁰ Later, we have also argued that impaired energy metabolism of the heart in diabetes may be traced to a substrate-induced inhibition of the Krebs cycle.⁷⁷

The effects of type 2 diabetes on myocardial energy metabolism are complex, because circulating levels of insulin, glucose, and NEFA are usually increased in this condition. Until recently, it has been assumed that the interactions of glucose and fatty acids proposed by Randle et al⁴² account for the correlation of lipids and reduced insulin sensitivity. There are now, however, several lines of evidence to suggest that elevated tissue lipid availability activates pathways that lead to the attenuation of insulin signals and impaired glucose uptake in diabetic muscle (Figure 2).^{68,81} Logic suggests one factor influencing the heart's adaptation to energetic stress in NIDDM would be the integrity of the cardiac insulin response system. As discussed above, in skeletal muscles of diabetic subjects, this system is functionally impaired because of genetic-environment interactions.^{81–86} Although the impact of type 2 diabetes on the insulin response system of the myocardium is less well characterized, it may differ from the phenotype exhibited by the skeletal muscles. Studies using 18F-fluorodeoxyglucose PET to compare insulin's effect on glucose uptake by heart and limb muscles in type 2 diabetic subjects have suggested preserved insulin responsiveness of the former in the face of insulin resistance in the latter.⁸⁷ To the extent that the myocardium continues to express a competent insulin response system in type 2 diabetes, therapeutic augmentation of oxidative glucose metabolism might be useful strategies for increasing the energy reserves of the failing diabetic heart. Clinical data to support this approach are now emerging.⁸⁸ It is important to emphasize that the above-mentioned studies refer to insulin responsiveness (ie, response of the heart to pharmacodynamic doses of insulin). To date, no studies have investigated insulin sensitivity (ie, response to physiological concentrations of insulin) in the human heart.

Although a variety of specific metabolic defects have been described in individuals or families with diabetes,⁷² studies by Shulman and colleagues,^{81,82} Rothman et al,⁸³ and Cline et al⁸⁴ using 31P and 13C nuclear magnetic resonance spectroscopy to track glucose through its intracellular metabolic pathways in vivo have established that the insulin resistance of diabetic skeletal muscle is primarily due to impaired glucose transmembrane transport and phosphorylation. Healthy offspring of patients with diabetes already exhibit impaired insulin stimulation of skeletal muscle glucose up-

take, suggesting the defect in glucose transport is genetically influenced.⁸⁵ The existence of such a defect in heart muscle requires further exploration.

Insulin Resistance: Cause and/or Consequence of Heart Failure

As outlined in this review, insulin resistance is an important risk factor for the development of cardiovascular diseases, including hypertension, left ventricular dysfunction, and heart failure. Conversely, heart failure causes insulin resistance and is associated with increased risk for the development of type 2 diabetes.^{89,90} As with the development of cardiovascular disease due to impaired insulin signaling, the development of insulin resistance in the heart failure patient is likely multifactorial. Possible mechanisms by which heart failure causes insulin resistance include sympathetic overactivity, loss of skeletal muscle mass, sedentary lifestyle of the patient, endothelial dysfunction with reduced skeletal muscle blood flow, and a potential effect of increased circulating cytokines, such as TNF α , on peripheral insulin sensitivity.^{91–96} A vicious cycle is therefore set in motion, in which heart failure and insulin resistance worsen one another. If this cycle is not broken by treatment of the heart failure (eg, with ACE inhibitors) or insulin resistance (eg, with thiazolidinediones), either alone or in combination, heart and end-organ function will deteriorate. This hypothesis, however, still needs to be tested.

Summary and Outlook

The effects of diabetes on the cardiovascular system include adaptive and maladaptive responses in the myocardium. We propose that altered metabolism and impaired insulin action in heart and skeletal muscle are both cause and consequence of altered cardiac function. Although heart disease in diabetes is characterized by extraordinary complex vascular, neurohumoral, and myocardial interactions, new paradigms begin to emerge. These paradigms include metabolic control of cardiac gene expression, lipotoxicity, glucotoxicity, and glucolipotoxicity. These topics are discussed in the second part of the review.

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