
Cardiac metabolism in the diabetic patient

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Conflicts of interest: None.

Abstract

Both clinical and experimental studies have pointed to a diabetic cardiomyopathy in humans that produces abnormalities in ventricular structure and function, independent of coronary artery disease or hypertension. A large body of evidence now indicates that metabolic perturbations and development of a cardiomyopathic phenotype are intimately related. In the diabetic heart, glucose oxidation is decreased and fatty acid oxidation is increased. This arises from the interplay of depressed insulin signaling with associated consequences in the control of myocardial glucose uptake and utilization, and increased circulating free fatty acids. Excessive reliance on fatty acid oxidation for ATP production results in greater costs in mitochondrial oxygen consumption. Fatty acids can also induce uncoupling of mitochondria, probably by upregulation of uncoupling proteins. Activity of uncoupling proteins decreases the mitochondrial proton gradient without the generation of ATP, and thereby decreases myocardial energy production. Defects in energy metabolism in the heart are likely to impair energy-requiring processes and therefore myocardial function, cardiac contractile performance, and diastolic function, the latter being a hallmark phenotype of diabetic cardiomyopathy at the earlier stages. This may also limit the ability of the myocardium in patients with type 2 diabetes to withstand ischemia, and may contribute to the increased cardiovascular morbidity and mortality in such patients.

■ *Heart Metab.* 2010;46:11–15.

Keywords: Cardiac energy metabolism, diabetes, fatty acid utilization, mitochondrial uncoupling, ventricular dysfunction

Introduction

Cardiovascular disease largely accounts for the 2-fold increase in mortality associated with type 2 diabetes. Since Rubler and colleagues [1] first suggested the existence of *diabetic cardiomyopathy* on the basis of postmortem findings in only four adult patients, general agreement has emerged on the type of heart disease that is associated with diabetes mellitus. Both clinical and experimental studies [2–4] have indeed pointed to a diabetic cardiomyopathy in humans that produces abnormalities in ventricular structure and function, independent of coronary artery disease or

hypertension. In particular, diabetes is now well recognized as a risk factor for the development of heart failure. Men with diabetes are more than twice as likely to have heart failure than those without the disease, and diabetic women have an even greater risk [5]. Heart failure can affect diastolic function or systolic function, or both. Although little is known about the pathogenesis of diabetic cardiomyopathy, a large body of evidence indicates that it is related to derangements in myocardial energy metabolism [6,7].

The aim of this short review is to summarize our current understanding of the complexity of

cardiac abnormalities that accompany diabetes, with a special emphasis on the relationship between metabolic perturbations and the development of a cardiomyopathic phenotype. An understanding of the effects of these metabolic disturbances on cardiac myocytes should be useful in optimizing therapeutic strategies to influence myocardial function favorably.

Cardiac energy metabolism in diabetes

In the normal adult heart, myocardial energy substrate preference varies in a dynamic manner to fulfill the tremendous energy needs. Whereas mitochondrial fatty acid oxidation is the chief source of energy, the relative contribution of glucose utilization pathways is significant, allowing the plasticity necessary for permanent cellular energy (ATP) production in the mitochondria in the context of diverse physiologic and dietary conditions. However, in the diabetic heart, utilization of carbohydrates is decreased and fatty acid oxidation is increased (Figure 1). The

increased reliance on fatty acid oxidation arises from the interplay of depressed insulin signaling with associated consequences in the control of myocardial glucose uptake and utilization, and increased circulating free fatty acids. Few studies have assessed insulin-stimulated glucose metabolism in the myocardium of patients with diabetes. Those studies that have used positron emission tomography to determine insulin-stimulated fluorine-18-labeled fluorodeoxyglucose uptake have clearly shown that type 2 diabetes is specifically associated with severe insulin resistance, regardless of coronary artery disease and despite normal basal blood flow [8,9].

Compared with glucose oxidation, reliance on fatty acid oxidation for ATP production results in higher costs in mitochondrial oxygen consumption, and calculations of the yield of ATP per oxygen atom consumed (P/O ratios) show that fatty acids are a less efficient fuel when compared with glucose. Therefore, more oxygen is required for ATP production when hearts are metabolizing fatty acids than when they utilize glucose. However, the theoretical difference in

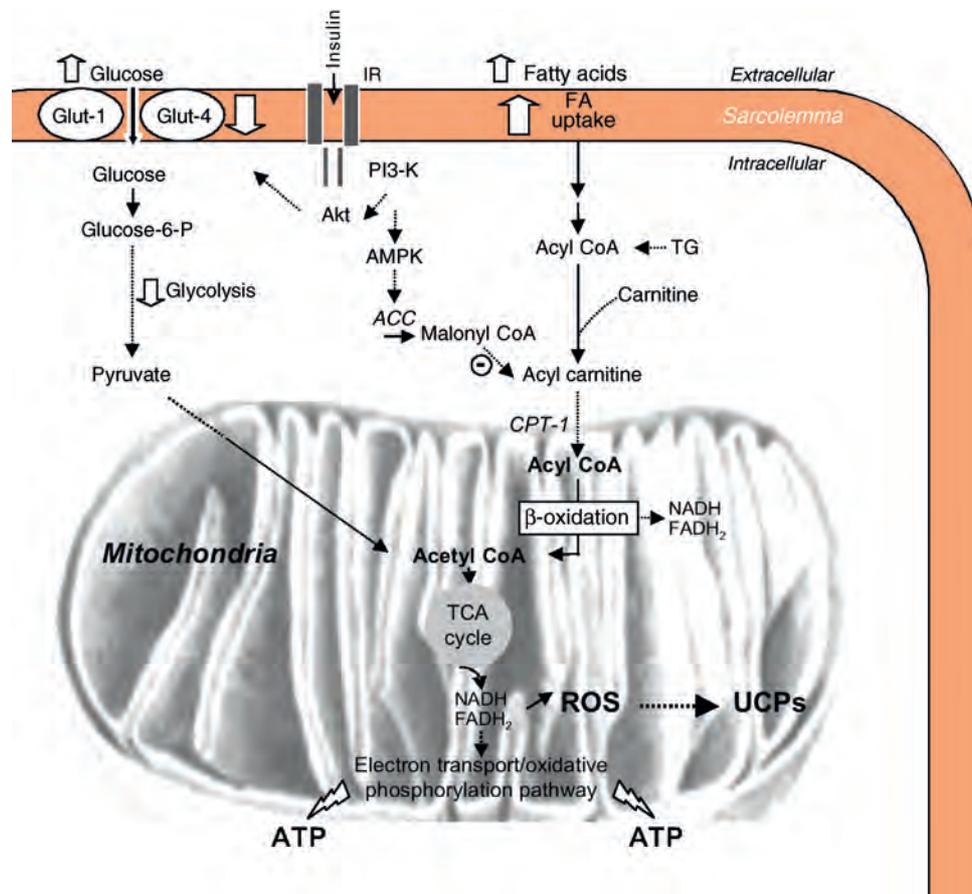


Figure 1. Schematic diagram showing cardiac myocyte energy metabolism. Fatty acids and glucose oxidation are the main ATP-producing pathways. In the uncontrolled diabetic state, because of the combined effects of insulin resistance and high circulating concentrations of fatty acids, glucose oxidation is decreased and fatty acid oxidation is increased. ACC, acetyl coenzyme A (CoA) carboxylase; Acyl carnitine, long-chain acyl carnitine; Acyl CoA, long-chain acyl CoA esters; Akt, also known as protein kinase B; AMPK, 5'-AMP-activated protein kinase; CPT-1, carnitine palmitoyl transferase-1; FA, fatty acid; IR, insulin receptor; PI3-K, phosphatidylinositol 3-kinase; ROS, reactive oxygen species; TCA, tricarboxylic acid cycle; TG, triglycerides; UCPs, uncoupling proteins.

cardiac efficiency based on calculations of P/O ratios for fat and glucose metabolism still appears greater than expected when the utilization of lipid is increased [10]. This observation feeds the argument that fatty acids can induce uncoupling of mitochondria, perhaps by upregulation of the expression and activity of uncoupling proteins. Uncoupling proteins are mitochondrial transporters present in the inner membrane of mitochondria. They belong to the family of anion mitochondrial carriers including adenine nucleotide transporters. The term "uncoupling protein" (UCP) was originally used for UCP1, which is uniquely present in mitochondria of brown adipocytes [11]. UCP1 catalyzes a highly regulated proton leak, converting energy stored within the mitochondrial proton electrochemical potential gradient to heat. This uncouples fuel oxidation from conversion of ADP to ATP, resulting in decreased synthesis of ATP [12]. Two uncoupling protein isoforms, UCP2 and UCP3, are located in the heart [13]. The expression of mitochondrial UCP2 and UCP3 that are present in human hearts correlates positively with fasting concentrations of plasma free fatty acids [13]. In parallel, there is a decrease in the concentrations of insulin-responsive glucose transporter (GLUT-4) protein.

It is also worth noting that fatty acids reduce insulin action by inhibiting insulin signaling pathways [14], leading to a decrease in glucose transporter function and further reduction in glucose oxidation. Work from a number of sources [15,16] supports the notion that fatty acids play a critical role in triggering the development of cellular insulin resistance through derangements in the insulin signaling cascade. Insulin signaling is mediated by complex multiple pathways characterized by spatial and temporal factors [17,18]. Binding of insulin to the insulin receptor stimulates the tyrosine kinase activity of the insulin receptor, leading to its autophosphorylation and to the subsequent phosphorylation of insulin receptor substrate. Studies have suggested that local accumulation of fat metabolites inside skeletal muscle, such as accumulation of fatty acyl coenzyme A (CoA), induces the activation of atypical protein kinase C (PKC- θ), a serine/threonine kinase that phosphorylates and subsequently activates another kinase, $\text{I}\kappa\text{B}$ kinase [14]. $\text{I}\kappa\text{B}$ kinase in turn phosphorylates serine residues on insulin receptor substrate, inhibiting its ability to bind SH2 domains of the p85 regulatory subunit of the lipid kinase, phosphatidylinositol 3-kinase (PI3-K). This results in impaired insulin signal transduction. As a consequence, the recruitment of GLUT-4 transporters to the plasma membrane, and therefore glucose uptake, is compromised. Although this mechanism is active in skeletal muscle and adipose tissue, it has been less clear whether similar mechanisms are apparent in cardiac muscle. This appears likely, since cellular accumulation of long-chain fatty acyl

derivatives such as long-chain acyl CoA has been shown to occur [19]. Another role for increased fatty acid concentrations is the attenuation of insulin regulation of 5'-AMP-activated protein kinase (AMPK) [20]. AMPK is a heterotrimeric enzyme that acts as a key "metabolic switch" in the heart in the control of glucose and fatty acid oxidation. AMPK also phosphorylates and inactivates key enzymes involved in ATP-consuming pathways. In the heart, AMPK stimulates fatty acid oxidation by inactivating acetyl CoA carboxylase and so decreasing the concentration of malonyl CoA, which inhibits the entry into, and the subsequent oxidation of long-chain fatty acids in, the mitochondria [21]. Interestingly, it has been shown that AMPK activation is antagonized by insulin [20]. The anti-AMPK effect of insulin is wortmannin-sensitive, like most short-term effects of insulin, suggesting that it is mediated by PI3-K. Therefore, the metabolic consequence of the interaction between insulin and AMPK is normally to increase the concentration of malonyl CoA, and consequently to limit fatty acid oxidation while facilitating glucose oxidation. This may be blunted by the presence of high plasma concentrations of fatty acids in diabetes [22].

Metabolic disturbances and left ventricular dysfunction in hearts of diabetic patients

An important question that arises relates to the mechanistic link(s) between altered myocardial energy metabolism and cardiac dysfunction in the diabetic heart. In the context of high-level fatty acid uptake, lipid intermediates accumulate within cardiac myocytes [19]. Experimental data indicate that increases in long-chain acyl CoA esters and fatty acids directly link metabolism to ATP-dependent potassium (K_{ATP}) channels in the heart [23]. Long-chain acyl CoA esters facilitate opening of K_{ATP} channels by reducing ATP sensitivity. The effects of the acyl CoA esters on K_{ATP} channels in cardiac myocytes may be functionally important, because long-chain fatty acids, particularly C_{16} and C_{18} fatty acids, serve as the main metabolic substrates of the heart, especially for the diabetic heart. The metabolizable form of these fatty acids is that of acyl CoA esters, which are synthesized at the outer mitochondrial membrane via acyl CoA synthetase, imported into the mitochondria, and subsequently metabolized via β -oxidation. However, as excessive concentrations of long-chain acyl CoA ester are present in the diabetic heart [19], it is tempting to speculate that this may favor opening of cell membrane K_{ATP} channels. The resulting shortening of the action potential would lead to a reduction in transsarcolemmal Ca^{2+} influx [23]. This, together with a deficiency of cardiomyocyte Ca^{2+} handling, in particular an increased Ca^{2+} leakage from the

sarcoplasmic reticulum – such as has been shown in hearts from type 2 diabetic *db/db* mice [24] in which the natural progression of diabetes is similar to the pathogenesis of type 2 diabetes in humans – may well subsequently lead to a reduction in myocardial contractility. Another, often unappreciated, but important feature of diabetic heart disease, particularly in type 2 diabetes, is a disproportionate increase in left ventricular mass [3,25]. Because diabetes is a strong risk factor for the development of heart failure, and given that left ventricular hypertrophy has been detected in a significant proportion of patients with type 2 diabetes [3,25], the role of cardiac sarcolemmal Na^+ – H^+ exchanger (NHE isoform 1) activity, which is involved in molecular mechanisms of hypertrophy, has been examined. This exchanger contributes significantly to the integrated control of intracellular pH in myocardial cells [26], and therefore directly links the cardiac metabolic state to ionic homeostasis. Recent data on a type 2 diabetic animal model have contributed to shedding light on the central role that NHE1 may play in favoring left ventricular hypertrophy in patients with type 2 diabetes, particularly under conditions of impaired myocardial perfusion and therefore myocardial ischemia in some circumstances [27,28].

Reliance on fatty acid oxidation for the production of ATP, which results in higher costs in mitochondrial oxygen consumption compared with glucose oxidation, may also contribute to ventricular dysfunction [29]. In this context, the activity of UCP2 and UCP3 proteins lowers the mitochondrial proton gradient without the generation of ATP and thereby decreases myocardial energy production. This process could explain why human phosphocreatine to ATP ratios correlate negatively with plasma free fatty acid concentrations [13]. It should be noted here that patients with heart failure also have increased plasma free fatty acid concentrations, high whole-body insulin resistance, and low insulin-stimulated fluorodeoxyglucose uptake in the heart [13,30,31]. A study of mitochondrial energetics in hearts of leptin-receptor-mutant (*db/db*) type 2 diabetic obese mice has demonstrated that mitochondrial uncoupling is indeed mediated by activation of uncoupling proteins [32]. This probably occurs on the basis of increased delivery of the reducing equivalents FADH_2 and NADH from fatty acid oxidation, coupled with a reduced ability for complete oxidation of these equivalents. This might contribute to increased generation of mitochondrial reactive oxygen species, which, in turn, activates uncoupling proteins. Mitochondrial uncoupling may *initially* represent an adaptive response to increased fatty acid oxidation and fatty-acid-mediated generation of reactive oxygen species. However, it does not completely normalize the overproduction of mitochondrial reactive oxygen species, as demonstrated

by the accumulation of products of lipid peroxidation [32]. Therefore, the negative impact of mitochondrial uncoupling is to reduce the mitochondrial supply of ATP. Altered myocardial energetics characterizes these hearts, and clearly precedes measurable alterations in in-vivo cardiac function, as assessed by echocardiography [32,33]. Cardiac high-energy phosphate metabolites, measured at rest in patients with type 2 diabetes using phosphorus-31 nuclear magnetic resonance spectroscopy, have revealed a decrease in phosphocreatine to ATP ratios [33]. Furthermore, data have underlined that, not only do alterations in cardiac energetics occur early in the pathophysiology of type 2 diabetes, but these alterations are correlated negatively with the fasting plasma free fatty acid concentrations.

Conclusion

Defects in energy metabolism in the heart are likely to impair energy-requiring processes and therefore myocardial function, cardiac contractile performance, and diastolic function [7], the latter being a hallmark phenotype of diabetic cardiomyopathy at the earlier stages. This may also limit the ability of the myocardium in patients with type 2 diabetes to withstand ischemia, and may contribute to the increased cardiovascular morbidity and mortality in such patients [34]. Manipulation of the myocardial metabolic substrate, aimed at shifting energy substrate preference from the use of fatty acids towards the use of glucose, as can be achieved with trimetazidine treatment [35,36], or at improving the coupling between fatty acid delivery and oxidation in cardiomyocytes to limit the production of reactive oxygen species, could be of benefit to the heart of diabetic patients. Interestingly, and of particular note, is the recent observation that part of the positive effects of trimetazidine on cardiac function might also be related to improved glucose homeostasis and insulin sensitivity [37]. ■

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