

Taking Diabetes to Heart—Deregulation of Myocardial Lipid Metabolism in Diabetic Cardiomyopathy

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Diabetic Cardiomyopathy

Hear disease is the leading cause of death in patients with diabetes.¹ Although advances in medical management and lifestyle interventions have reduced cardiovascular mortality in diabetic patients by as much as 40% over the last decade, the actual number of deaths is predicted to rise as a result of the obesity epidemic (which is clinically linked to diabetes) and an aging population.¹ The underlying causes of cardiovascular dysfunction in diabetes are complex and include increased susceptibility to atherosclerosis, vascular dysfunction, dyslipidemia, hypertension, and the prothrombotic state.^{2–7} Furthermore, the results of Framingham, Strong, and other large epidemiologic studies showed that the incidence of cardiomyopathy is higher in diabetic patients even after adjustment for hypertension, microvascular disease, hypercholesterolemia, body mass index, and other risk factors.^{8–12} The impairment of left ventricular function in a diabetic patient without underlying coronary artery disease or hypertension is now recognized as a distinct clinical entity termed “diabetic cardiomyopathy.”^{13,14}

Diabetic cardiomyopathy in humans is characterized by diastolic dysfunction, which is often followed by the development of systolic dysfunction.¹⁵ Echocardiographic analysis of patients with type 1 diabetes mellitus (T1DM) and no microvascular or macrovascular disease revealed increased left ventricular thickness and left ventricular end-diastolic diameter, whereas the ejection fraction was reduced.¹⁶ In a similar study of patients with type 2 diabetes mellitus (T2DM), the prevalence of diastolic dysfunction was as high as 30%.^{17–19}

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Various rodent models of diabetes have been developed, including streptozotocin-induced destruction of pancreatic β cells, genetic deletion of leptin (*ob/ob*) or leptin receptor (*db/db*) in mice, Zucker fatty rat strain, and others. Moreover, wild-type mice fed a high-fat diet (Western diet) develop obesity and insulin resistance reminiscent of T2DM and metabolic syndrome in humans.^{20,21} Notably, all these animal models develop various degrees of cardiac dysfunction that starts, similar to in human patients, with ventricular thickening and diastolic defects and may eventually progress to systolic dysfunction.²⁰ It is important to note that rodents are resistant to atherosclerosis and hypertension even in the setting of disrupted insulin signaling or lipid homeostasis. Although there is still considerable debate regarding human diabetic cardiomyopathy as a discrete disorder or as a complication of diabetic comorbidities (eg, hypertension, elevated triglycerides), the presence of cardiac dysfunction in these animal models strongly argues for a direct pathophysiologic link between diabetes and heart disease and also allows for the study of diabetic cardiomyopathy without the confounding factors commonly present in human studies.

In the diabetic heart, there is significant disruption of molecular processes essential for normal cardiac function. First, calcium signaling is impaired, leading to altered relaxation-contraction dynamics and the resultant diastolic and systolic dysfunction.^{22–24} Second, the diabetic heart shows signs of increased oxidative stress, which damages structural components of the heart and activates signaling pathways such as NF- κ B, c-Jun N-terminal kinases, and p38 mitogen-activated protein kinases through oxidative modifications to select residues.^{25–27} Third, endoplasmic reticulum stress and accumulation of unfolded proteins exert significant toxicity and eventually lead to cardiomyocyte apoptosis.^{28,29} Finally, disruption in cytokine signaling and low-grade inflammation of the heart further repress cardiac function in diabetes.³⁰ In addition to these pathways, diabetic cardiomyopathy is being exceedingly recognized as a metabolic disease of the heart characterized by increased reliance on fatty acids (FAs) compared with glucose as a source of energy, and the resulting maladaptive changes of this metabolic switch will be highlighted in this review.

Diabetic Cardiomyopathy as a Metabolic Disease of the Heart

Derangements in cardiac lipid and glucose metabolism are becoming recognized as an early event in the deterioration of heart function in diabetes. To sustain continuous contractions, the human heart consumes the largest amount of energy per gram of tissue in the body, about 6 kg of ATP, or ≈ 20 times its own weight, per day.³¹ This energy can be generated from a variety of substrates, such as fat, carbohydrate, protein, ketone bodies, or lactate, with 95% of total energy being derived from mitochondrial oxidative phosphorylation of fatty acids and glucose.^{32–34} Oxidation of fatty acids amounts to $\approx 70\%$ of all ATP produced by the heart under resting conditions, whereas increased work load such as exercise or adrenergic stimulation increases the relative contribution of glucose to this process.^{32,35} Moreover, the inherent flexibility of the heart to use different types of fuel is critical for maintaining consistent ATP production with ever-changing metabolic substrate availability.

In diabetic hearts, there is a dramatic shift away from glucose utilization and almost complete reliance on FAs as the energy source, resulting in loss of metabolic flexibility. In human patients with T2DM and heart failure, a dramatic accumulation of lipids within the myocardium and restructuring of the lipid metabolic gene expression profile were observed.³⁶ In addition, McGavoc et al found intramyocardial lipid deposits in diabetic patients with normal cardiac function, suggesting that metabolic disturbances may precede the onset of left ventricular dysfunction.³⁷ Functionally, positron emission tomography studies of human patients with T1DM revealed increased myocardial FA utilization, with a concurrent reduction in glucose oxidation,^{38,39} and similar findings were obtained in patients with T2DM.⁴⁰

Similar to human patients, rodent models of T1DM and T2DM exhibit striking intramyocardial lipid accumulation, as well as an approximately 2-fold increase in fatty acid oxidation and a decrease in glucose use.^{41–43} To better understand the contribution of metabolic remodeling to the development of diabetic cardiomyopathy, mouse models with disruption of select regulatory points in FA and glucose metabolism were created and studied. It was shown that a decrease in glucose utilization is detrimental to the heart, as mice with heterozygous deletion of glucose transporter 4 (GLUT4+/-) and subsequent reduction in glucose delivery to the cardiomyocytes increased their use of FAs as an energy source and developed a cardiac phenotype resembling diabetic cardiomyopathy in humans.⁴⁴ On the other hand, overexpression of GLUT4 in diabetic *db/db* mice increased glucose delivery to the heart and reduced its use of FAs and was protective against the development of cardiac dysfunction.⁴² An increase in FA utilization by the

heart through targeted cardiac-specific overexpression of human lipoprotein lipase and increased uptake of FAs from circulating very-low-density lipoproteins led to cardiac lipid accumulation and the development of dilated cardiomyopathy.⁴⁵ A similar phenotype of cardiac steatosis and reduced heart function was observed in other mouse models of increased FA utilization either by cardiac-restricted transgenic expression of long-chain acyl coenzyme A (CoA) synthetase 1 involved in FA transport across membranes,⁴⁶ FA transport protein 1 (FATP),⁴⁷ or peroxisome proliferator-activated receptor α (PPAR α) transcription factor, which upregulates the expression of genes involved in FA uptake and oxidation.⁴⁸ Thus, the switch from glucose to FA oxidation is an important determinant in the development of diabetic cardiomyopathy.

Fatty Acid Metabolism in the Heart

The heart has a limited capacity for de novo synthesis of FAs; thus, it primarily relies on the exogenous supply of FAs from circulation, including albumin-bound free FAs and triglyceride (TAG)-rich lipoproteins.^{49,50} The rate of FA uptake by the heart is not primarily under hormonal control and instead is largely determined by the arterial FA concentration, which can range from very low levels in fetal circulation to >2 mmol/L in an adult with uncontrolled diabetes and metabolic syndrome.^{32,51}

Although free FAs can translocate into the cardiomyocyte through passive diffusion across the plasma membrane, this mechanism demonstrates slow kinetics and is inhibited by proteases.⁵² To facilitate FA uptake, the heart has a protein-mediated carrier system consisting of 3 FA transporters: CD36, FATP, and the plasma membrane form of FA-binding protein.⁵³ Of these potential carriers, CD36 plays a major role in the translocation of FAs across the sarcolemmal membrane of cardiac myocytes.⁵⁴ Indeed, studies in CD36-knockout mice demonstrated that CD36-mediated transport is responsible for up to 70% of FA uptake into contracting cardiomyocytes.⁵⁵ Furthermore, patients with CD36 deficiency have low rates of myocardial FA tracer uptake, consistent with a key role for CD36 in regulating cardiac FA metabolism in vivo.⁵⁶ Approximately 50% of cellular CD36 is stored in intracellular vacuoles where it can be recruited to the sarcolemmal membrane to facilitate FA uptake.⁵⁷ Muscle contraction, insulin, and several pharmacological agents, including caffeine and phenylephrine, stimulate CD36 translocation to the sarcolemmal membrane, thereby facilitating FA uptake.⁵⁸

After uptake by the cardiomyocyte, approximately 75% of cytosolic FAs is transferred into the mitochondria and oxidized for ATP generation, whereas the remainder is converted to TAG for storage that can be rapidly mobilized

for energy purposes based on cellular demand.⁵⁹ Long-chain FAs cannot freely enter the mitochondria and must be first esterified into fatty acyl CoA by cytosolic fatty acyl CoA synthetase (FACS). Studies have demonstrated that FACS is associated with CD36 or FATP on the cytosolic side of the sarcolemmal membrane, suggesting that FACS also influences FA uptake.⁶⁰ Consistent with this finding, overexpression of FACS in the heart or fibroblasts causes increased FA uptake and intracellular TAG accumulation.⁶¹ The fatty acyl CoAs are then converted to acylcarnitine by carnitine palmitoyltransferase-1 (CPT1) and transported across the inner mitochondrial membrane by a carnitine-acylcarnitine translocase that exchanges acylcarnitine for carnitine.⁶² Finally, mitochondrial FAs undergo β -oxidation to yield acetyl CoA, which is then fed into the tricarboxylic acid cycle for ATP production (Figure 1). The generation of acetyl CoA and 3 NADH from β -oxidation also decreases glucose oxidation via the activation of pyruvate dehydrogenase kinase (PDK) and the subsequent phosphorylation and inhibition of the pyruvate dehydrogenase (PDH) enzyme complex, allowing the heart to switch sources for energy production based on nutritional status. This relationship between FA and glucose metabolism, first described by Philip Randle in 1963, is known as the glucose-FA cycle or the Randle cycle.⁶³

Enzymes involved in FA transport and oxidation are under a high degree of transcriptional control, particularly by the

nuclear receptor transcription factor superfamily known as the PPARs, with PPAR α the dominant isoform in the heart.⁶⁴ Activation of PPAR α promotes the expression of genes that mediate nearly every step of FA oxidation, including FA uptake (CD36, FATP), cytosolic FA binding, FA esterification (FACS), malonyl-CoA metabolism (malonyl-CoA decarboxylase), mitochondrial FA uptake (CPT1), FA β -oxidation (very-long-chain acyl CoA dehydrogenase, long-chain acyl CoA dehydrogenase; medium-chain acyl CoA dehydrogenase; 3-ketoacyl-CoA thiolase), mitochondrial uncoupling (mitochondrial thioesterase 1), and glucose oxidation (pyruvate dehydrogenase kinase 4 [PDK4]; for a review, see reference 65). The end result of PPAR α activation is increased breakdown of fats via increased FA flux into the cell and upregulation of enzymes involved in FA β -oxidation.⁴⁸ Another PPAR isoform, PPAR γ , is expressed in the heart, and its activation is associated with increased insulin-stimulated glucose uptake by peripheral tissue and reduced hepatic gluconeogenesis.^{66,67} However, the use of certain forms of glitazones, which are PPAR γ agonists, is associated with edema, plasma volume expansion, and the development of congestive heart failure, thus limiting their use.^{68,69}

Alterations in Lipid Homeostasis in the Diabetic Heart

That both T1DM and T2DM are associated with lipid accumulation and cardiac dysfunction^{21,70} is suggestive of a common molecular mechanism for these diseases. In fact, the underlying pathways for the 2 disorders appear to converge at the point of increased delivery and utilization of FA for ATP production, although the primary reasons for the overreliance on lipid as an energy source are distinct.

Early Steps of Metabolic Derangement in T1DM and T2DM

Studies of human patients with T1DM have shown that their hearts remain responsive to some of the actions of insulin⁷¹; however, their cardiac glucose uptake is dramatically impaired because of the lack of insulin production.^{72,73} Insulin stimulates glucose uptake by inducing transcription of the GLUT4 glucose transporter in metabolically active tissues such as liver, heart, skeletal muscle, and adipocytes. In addition, activation of insulin signaling triggers translocation of GLUT4-containing cytoplasmic vesicles to the plasma membrane, thus bringing the transporter to its site of action.^{74,75} In streptozotocin-induced T1DM animals, GLUT4 levels were significantly reduced in cardiac and skeletal muscle,^{76,77} accounting for the low rates of cardiac glucose uptake that force cardiomyocytes to rely heavily on FAs as

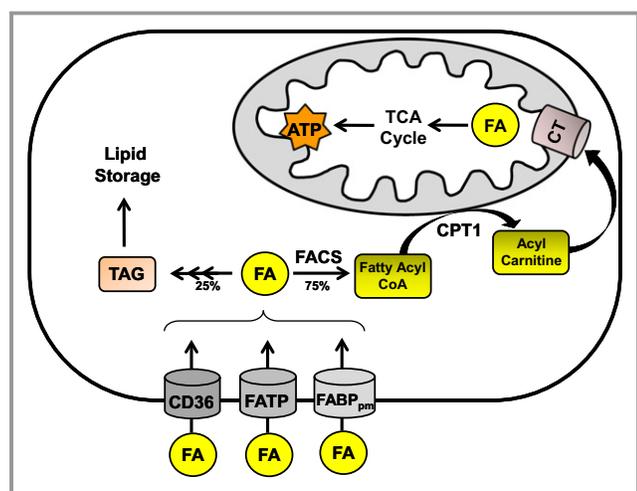


Figure 1. Overview of myocardial fatty acid (FA) metabolism. FAs are imported into the cell by various FA transporters, including CD36, FA transport protein (FATP), and plasma membrane FA-binding protein (FABP_{pm}). Imported FAs may be stored as triglyceride (TAG) or converted to fatty acyl CoA by FA CoA synthase (FACS). The acyl group of fatty acid CoA can be transferred to carnitine via carnitine palmitoyltransferase (CPT) 1. The acylcarnitine is then shuttled into the mitochondria by carnitine translocase (CT), where it can undergo β -oxidation, producing acetyl CoA, which can be used in the tricarboxylic acid (TCA) cycle to produce adenosine triphosphate (ATP).

their energy source in the absence of insulin. Notably, ample amounts of fat are available to the heart in T1DM because of enhanced lipolysis in adipose tissue, which is normally inhibited by insulin.⁷⁸

Although GLUT4 expression was also shown to be reduced in the hearts of T2DM patients,⁷⁹ functional studies of their myocardium revealed preservation of insulin sensitivity and no impairment in glucose uptake in response to insulin.^{80,81} Moreover, in the *db/db* mouse model of T2DM, reduced cardiac glucose oxidation and increased reliance on FAs preceded the development of insulin resistance and hyperglycemia,⁸² suggesting that insulin resistance was not the primary mechanism for the metabolic switch. It is well recognized that circulating FA and TAG levels are significantly elevated in patients with T2DM and metabolic syndrome.^{83,84} This is because of increased consumption of FAs as a part of the Western diet, which exceeds adipose tissue capacity for fat storage, increased lipolysis of stored fat, and enhanced very-low-density lipoprotein secretion by the liver. Unlike glucose, whose entry into cardiomyocytes is tightly controlled by insulin action and the presence of GLUT4 on the sarcolemmal membrane, FA uptake into the heart is not hormonally regulated and is largely driven by the availability of lipids in the bloodstream.⁵³ As a result of high circulating lipid content, the type 2 diabetic heart takes in disproportionately more FAs and suppresses glucose uptake,⁸⁵ as oxidation of FAs that are already present in the cell is sufficient to maintain normal ATP levels. This results in almost 100% reliance on FAs as the energy source.

In summary, the type 1 diabetic heart is glucose-starved and forced to oxidize FAs as an alternative substrate to maintain normal ATP levels. On the other hand, the heart in the T2DM patient is flooded with fat, leaving little room for glucose oxidation by the mitochondria. This paradigm is also supported by animal model studies, although it should be noted that differences in cardiac function exist among rodent models of T1DM and T2DM (Table 1).^{20,86–88} The end result, however, is the same: loss of metabolic flexibility through exclusive use of fat as the energy substrate.

Common Pathways for Cardiac Dysfunction in Diabetes

Once metabolic preference is given to FAs and the heart moves away from glucose oxidation, the downstream changes are similar between T1DM and T2DM. This metabolic switch is mediated by FAs, which activate several signaling cascades to match the rates of FA and glucose oxidation to the availability of these substrates in the cell. The changes induced by FAs in cardiomyocytes include inhibition of insulin receptor substrate 1 (IRS1), allosteric suppression of glycolytic enzymes, and transcriptional activation of fatty acid metabolism genes through PPAR α , which collectively lock the heart in a metabolically inflexible FA-dependent state.

IRS1 inhibition

Increased accumulation of FAs and their derivatives fatty acyl CoA, diacylglycerol (DAG), and ceramide dampens insulin signaling through activation of serine kinases such as protein kinase C, c-Jun N-terminal kinases, mammalian target of rapamycin, and inhibitor κ B kinase β .^{89–92} Insulin signaling requires phosphorylation of IRS1 by tyrosine kinase phosphatidylinositol 3-kinase (PI3K).⁹³ However, phosphorylation of residues adjacent to the PI3K binding sites by serine kinases displaces PI3K and thus interferes with its ability to activate IRS1.^{90,94} The inhibitory effect of free FAs on IRS1 and insulin signaling was demonstrated in cell culture,^{95,96} animal models,^{97–99} and human volunteers¹⁰⁰ and may contribute to the development of diabetes in patients with elevated plasma triglyceride levels.

Glycolysis inhibition

In addition to dampening insulin signaling, the products of mitochondrial FA oxidation have been shown to repress cellular glucose utilization through allosteric inhibition of key glycolytic enzymes. First, a high rate of FA oxidation increases the amount of acetyl-CoA and NADH relative to free CoA and NAD(+), respectively. Both these metabolites activate PDK4, an inhibitor of the PDH complex, thus preventing pyruvate

Table 1. Differences in Cardiac Function in Diabetic Humans and Among Rodent Models of Types I and II Diabetes

	Obese/Diabetic Patient	<i>ob/ob</i>	<i>db/db</i>	ZDF	STZ
Cardiac size	↑	↑	↑	↑	=
Systolic function	↓	↑↓	↓	↓	↓
Diastolic function	↓	↓	↓	↓	↓
LV hypertrophy	↑	↑	↑	↑	↑
Lipid content	↑	↑	↑	↑	↑
FA oxidation	↑	↑	↑	↑	↑

db/db indicates leptin receptor in mice; FA, fatty acid; LV, left ventricle; *ob/ob*, genetic deletion of leptin in mice; STZ, streptozotocin; ZDF, Zucker diabetic fatty. See text for references.

oxidation by the mitochondria.^{101,102} Consistently, increased PDK4 levels and activity were found in the hearts of diabetic rats¹⁰³ and in the skeletal muscle of mice fed a high-fat diet,¹⁰⁴ and cardiac glucose oxidation was also reduced in *db/db* and *ob/ob* mice.⁸²

Metabolic reprogramming by PPAR α

Another target of free FAs in cardiomyocytes is the PPAR α pathway. As discussed earlier, PPAR α is a transcription factor that increases cellular utilization of FAs by upregulating a subset of genes that promote FA uptake and β -oxidation, as well as suppressing glucose use through the induction of inhibitory proteins.^{105,106} Importantly, various saturated and unsaturated FAs were shown to bind to and activate PPAR α in ligand-binding assays,¹⁰⁷ establishing a direct link between elevated FA levels in cardiomyocytes and the induction of PPAR α signaling. An increase in PPAR α expression was reported in almost all rodent models of diabetic cardiomyopathy, including streptozotocin-induced T1DM,^{108,109} Zucker diabetic fatty rats,¹¹⁰ and *ob/ob* and *db/db* mice,¹¹¹ whereas deletion of the PPAR α gene protected mice against high-fat-diet-induced diabetes.^{112,113} The key role of PPAR α induction in the development of diabetic cardiomyopathy is exemplified by the study by Finck et al,⁴⁸ in which cardiac PPAR α overexpression in the mouse produced a phenotype that mimicked diabetic cardiomyopathy in the absence of systemic insulin resistance, hyperglycemia, or dyslipidemia. Importantly, the hearts from PPAR α transgenic mice exhibited increased rates of palmitate uptake and oxidation, reduction in glucose utilization, accumulation of intramyocardial lipid droplets, and diastolic dysfunction.⁴⁸

The downstream targets of PPAR α are significantly upregulated in diabetic hearts and were shown to be responsible for the development of cardiac dysfunction. Thus, in streptozotocin-induced diabetes there was a significant increase in the levels of CD36 and the plasma membrane form of FA-binding protein transporters,^{114,115} which are responsible for FA uptake into the cell across the plasma membrane. Moreover, in Zucker diabetic fatty rats¹¹⁶ and in diabetic mice induced by high-fat feeding,¹¹⁷ there was permanent relocalization of inactive CD36 and/or the plasma membrane form of FA-binding protein in cytoplasmic vacuoles to the plasma membrane, although the precise mechanism for this finding is unknown. Consistent with membrane localization of CD36, diabetic rats exhibited enhanced rates of FA uptake and lipid accumulation in the heart,^{115,118–120} whereas mice with genetic deletion of CD36 were protected against diet-induced insulin resistance.¹²¹ Notably, CD36-knockout hearts exhibited a reduction in FA oxidation and a compensatory increase in glucose oxidation.¹²² Although CD36-sufficient animals experienced

reduced insulin sensitivity and steady decline in heart function with aging, CD36-knockout mice had preserved rates of glucose oxidation and exhibited no drop in cardiac function with age.¹²³ Finally, deletion of CD36 in the hearts of PPAR α transgenic mice reduced myocardial TAG content, increased glucose oxidation rates, and restored their cardiac function.¹²⁴

Another target of PPAR α , CPT1, which functions in FA uptake into the mitochondria for β -oxidation, was shown to play a role in diabetic cardiomyopathy. In streptozotocin-induced diabetic rats, administration of the CPT1 inhibitor methyl palmoixirate in combination with triiodothyronine, prevented the development of cardiomyopathy and normalized the levels of long-chain acylcarnitines in the myocardium.¹²⁵ Similar results were obtained with another inhibitor of CPT1, etomoxir, which also increased cardiac glucose utilization.¹²⁶

Finally, in addition to facilitating FA uptake and β -oxidation, PPAR α also suppresses cellular glucose utilization, thus locking the cell in a FA-dependent, metabolically inflexible state. PDK4, an inhibitor of the key glycolytic enzyme PDH, was shown to be a direct target of PPAR α . A study of T1DM and T2DM rats reported increased PDK4 protein level and PDK activity in the heart,^{103,127} and similar upregulation of PDK4 was also shown in PPAR α transgenic mice.⁴⁸ Finally, PDK4 protein was elevated in the skeletal muscle of insulin-resistant human subjects¹²⁸ and in healthy human volunteers consuming a high-fat, low-glucose diet.¹²⁹ Consistent with the function of PDK4 in the regulation of glucose oxidation, mice with a targeted deletion of PDK4 in the heart had lower blood glucose levels and improved glucose tolerance compared with wild-type mice after a high-fat diet.¹³⁰ However, PDK4-overexpressing mice were also found to be resistant to high-fat diet through a novel mechanism involving the activation of AMPK and distinctive metabolic reprogramming.¹³¹ Although the exact contribution of PDK4 to diabetic cardiomyopathy remains to be determined, its upregulation in diabetic hearts appears to block the ability of the heart to use glucose as an energy substrate and thus further lock it into a metabolically inflexible state. Therefore, insulin resistance, lipid accumulation, overreliance on FA metabolism, and PPAR α dysregulation may all contribute to metabolic derangements, resulting in diabetic cardiomyopathy (Figure 2).

Molecular Pathology in the Diabetic Heart

The metabolic rigidity of the diabetic heart is a well-recognized phenomenon, but the exact mechanism by which overreliance on FAs for ATP production culminates in cardiac pathology remains a subject of intense debate. Several hypotheses have been proposed, including reduced efficiency

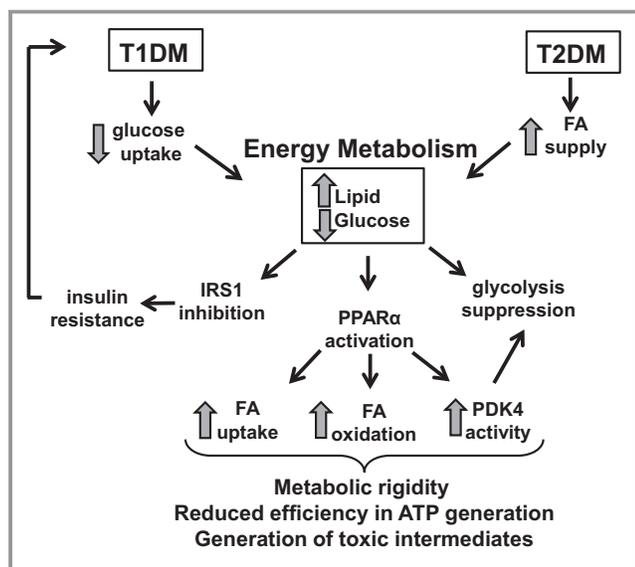


Figure 2. Pathophysiology of type 1 (T1DM) and type 2 (T2DM) diabetes mellitus on energy metabolism in the heart. Both T1DM and T2DM lead to insulin receptor substrate 1 (IRS1) inhibition, peroxisome proliferator-activated receptor α (PPAR α) activation, and suppression of glycolysis, resulting in metabolic rigidity, reduced adenosine triphosphate (ATP) generation efficiency, and generation of toxic fatty acid (FA) intermediates. PDK4 indicates pyruvate dehydrogenase kinase 4.

of a fat-burning heart and toxicity of FA metabolites accumulating in the myocardium.

Metabolic Inefficiency of FA Oxidation

Hearts from diabetic animals, such as *ob/ob* mice, consume $\geq 30\%$ more oxygen compared with nondiabetic hearts, while generating the same or even reduced amounts of contractile force.¹³² The reasons for this metabolic inefficiency of the diabetic heart are multiple and relate to the underlying disruption of energy balance. First, a substrate switch from glucose to FAs, even in the absence of pathology, was shown to reduce the efficiency of oxidative phosphorylation because of increased oxygen consumption.¹³³ The complete oxidation of 1 molecule of palmitate requires 46 atoms of oxygen and generates 105 molecules of ATP. On the other hand, glucose oxidation consumes 12 atoms of oxygen to produce 31 molecules of ATP. Thus, each molecule of ATP that came from the oxidation of FA costs ≈ 0.3 oxygen molecules more than the ATP generated from glucose.^{134,135} Several experimental studies in nondiabetic animals and humans supported the notion of reduced metabolic efficiency of fat oxidation in the heart. Perfusion of isolated mouse working hearts with high concentrations of free FAs resulted in increased myocardial oxygen consumption. Moreover, acute elevation of FA oxidation in a canine model achieved by intravenous infusion of a

heparin-TAG mixture also increased cardiac oxygen consumption by $\approx 25\%$ with no corresponding change in cardiac power output.^{136,137} A reduction in mechanical efficiency of the heart was also observed in healthy human volunteers with increased circulating free FAs achieved by infusion of a heparin-TAG mix.¹³⁸ Alternatively, boosting cardiac glucose oxidation was shown to reduce cardiac oxygen consumption and to improve cardiac efficiency, as exemplified by studies in pigs receiving intravenous infusions of a glucose-insulin cocktail.¹³⁹

Disproportional reliance on FAs for ATP generation not only requires more oxygen, but also alters other aspects of cardiac energetics, including cellular ATP shuttling, noncontractile energy expenditure, and mitochondrial coupling. Long-chain acyl CoA derivatives were shown to inhibit the adenine nucleotide translocator required for the transport of ATP from mitochondria to the cytosol,^{140–142} resulting in inefficient energy delivery to myofibrils and potentially affecting cardiac contractility. FA loading of the heart was also linked to the futile cycling of lipid intermediates, such as conversion of TAG to fatty acyl derivatives and back to TAG, presumably as a protective mechanism against free FA toxicity.¹³⁵ Although the relative contribution of this pathway to the overall energy expenditure of the diabetic heart is unknown, in isolated noncontracting cardiomyocytes, futile cycling of lipid derivatives was shown to consume up to 30% of total cellular energy.¹⁴³ Finally, the metabolic switch to FA utilization in diabetes was linked to mitochondrial uncoupling and reduction in mitochondrial membrane potential by uncoupling proteins (UCPs) 2 and 3. UCPs were originally identified in brown fat as proteins that dissipate mitochondrial proton gradient to generate heat, bypassing the ATP synthesis step and reducing mitochondrial energetic efficiency.¹⁴⁴ Upregulation and activation of UCP2 or UCP3 were reported in the hearts of *db/db* and *ob/ob* mice⁸² and streptozotocin-treated rats,¹⁴⁵ as well as in humans with increased circulating plasma free FAs. UCP2 and UCP3 were shown to be positively regulated by FAs, as intravenous infusion of lipid in nondiabetic lean Zucker rats resulted in elevated mRNA levels of UCP2 and UCP3 in the heart.¹⁴⁶ Moreover, treatment of cultured L6 myotubes or neonatal rat cardiomyocytes with free FAs significantly upregulated the expression of UCP3 and UCP2 proteins, respectively.^{147,148} The effects of FAs on UCP expression may be mediated by PPAR α , as pharmacologic activation of this transcription factor was shown to increase the levels of UCP3, whereas PPAR α knockout dramatically decreased UCP3 content in the mouse heart.^{149,150} Overall, overreliance on FAs as a metabolic substrate appears to increase oxygen consumption, uncouple the mitochondria, and alter energy transfer within the myocyte, disrupting the vital aspects of cardiac physiology.

Lipotoxicity

The dramatic accumulation of intramyocardial lipids in the diabetic heart led to the hypothesis of “toxic lipids” as mediators of cardiac dysfunction in diabetic cardiomyopathy,¹⁵¹ and the role of different lipid intermediates in the heart have since been examined. The accumulation of neutral lipids such as TAG positively correlated with body mass index and left ventricular hypertrophy in patients with obesity or impaired glucose tolerance, suggesting that they may play a role in deterioration of cardiac function.¹⁵² However, studies of mice transgenic for diacylglycerol acyltransferase 1 (DGAT1) in the heart displayed normal cardiac function despite increased accumulation of neutral TAG in the myocardium, suggesting that increased TAG content itself may not be toxic to the heart.¹⁵³ In fact, when crossed with a mouse model of diabetic cardiomyopathy through cardiac-restricted overexpression of ACS, DGAT1 overexpression actually protected the heart from dysfunction.¹⁵³ Thus, more toxic lipid intermediates, such as ceramide and DAG, have been implicated.

Accumulation of ceramide and DAG has been demonstrated to alter intracellular signaling pathways and promote apoptotic cell death.^{154,155} In addition to its structural role as a key component of the cell membrane, ceramide functions as an intracellular messenger that can trigger apoptosis by inducing the release of cytochrome c from the mitochondria.¹⁵⁶ Moreover, as mentioned earlier, ceramide and DAG desensitize the heart to insulin action by compromising tyrosine phosphorylation of the IRS and its ability to activate the PI3K/protein kinase B pathway involved in insulin signaling.¹⁵⁷

Inhibition of ceramide synthesis in transgenic mouse models of lipotoxic cardiomyopathy improves cardiac structure, function, and metabolism. For example, mice fed a high-fat diet and treated with fenretinide, an inhibitor of the rate-limiting enzyme in ceramide biosynthesis, had reduced tissue ceramide levels and increased insulin action.¹⁵⁸ In addition, the lipotoxic dilated cardiomyopathy of mice with cardiac-specific overexpression of glycosylphosphatidylinositol-anchored lipoprotein lipase was rescued by myriocin, a serine palmitoyl transferase I inhibitor that blocks the first enzyme in de novo ceramide synthesis.¹⁵⁹ In a clinical study conducted in Poland that assessed the apoptotic role of ceramides in the human heart, apoptotic markers were higher in the myocardium of obese and diabetic patients compared with lean patients. However, ceramide content remained stable among the groups, and mRNA levels of enzymes involved in both the synthesis and degradation of ceramides were increased in obese and diabetic patients compared with lean patients, suggesting that ceramide may not be the main factor in cardiomyocyte apoptosis in the setting of obesity or

diabetes.¹⁶⁰ Therefore, further research is needed to elucidate the role of ceramides in the development of lipotoxic cardiomyopathy.

In addition to ceramide, the toxic lipid intermediate DAG is known to accumulate in obesity and diabetes.¹⁶¹ DAG is a byproduct of lipolysis, derived from TAG hydrolysis via adipose TAG lipase. DAG is hypothesized to interfere with the cardiac insulin-signaling cascade by activating protein kinase C, leading to decreased glucose uptake.¹⁶² Cardiac overexpression of DGAT1, the enzyme that converts the toxic lipid intermediate DAG to TAG, in a lipotoxic mouse model, prevented cardiac dysfunction, despite increasing heart TAG levels.¹⁵³ In addition, mice fed a high-fat diet showed a decrease in insulin-stimulated glucose oxidation that was positively associated with increased myocardial DAG accumulation and decreased DGAT expression.¹⁶³ However, the effects of DAG on apoptosis remain to be elucidated.

Although the lipotoxic effects of FA accumulation in the heart have been demonstrated in animal models, limited evidence is available regarding the role of cardiac lipotoxicity in obese or diabetic humans. This issue is further complicated by the confounding effects of genetic and dietary variability, as well as risk factors such as physical inactivity, hypertension, and hyperlipidemia. Ventricular biopsies from type 2 diabetic patients demonstrate increased apoptosis, consistent with the activation of lipotoxic mechanisms, although the cause-and-effect relationship with toxic lipid species has not been established.¹⁶⁴ To further elucidate the role of cardiac lipotoxicity in humans, noninvasive *in vivo* imaging techniques to track TAG metabolism, such as [¹H] magnetic resonance spectroscopy, will become increasingly important.

Targeting FA Metabolism as a Therapeutic Intervention in Diabetic Cardiomyopathy

The strategy of targeting myocardial metabolism as a therapeutic intervention in the maintenance of cardiovascular health in diabetes is promising. Diabetic hearts exhibit increased FA oxidation, decreased glucose utilization, and decreased insulin sensitivity, and recent data indicate that these changes may be detrimental to cardiac function.⁷⁰ In addition to commonly used treatments in T2DM, such as PPAR agonists and metformin, myocardial substrate utilization can be modulated by indirect and direct approaches to decrease FA oxidation and increase glucose utilization. Indirect approaches are aimed at decreasing circulating FA levels, such as by the administration of glucose-insulin-potassium (GIK) solutions, nicotinic acid, glucagon-like peptide (GLP)-1 agonists, and β -adrenergic-blocking drugs. Direct approaches include inhibition of FA mitochondrial uptake via suppression of CPT1, the inhibition of enzymes involved in

β -oxidation, and activation of the PDH complex through inhibition of PDK (Table 2).

It is important to note that, although the concept of decreasing myocardial FA oxidation to increase glucose oxidation is appealing, the actual process of drug development is likely to be much more complicated. Targeting different points in metabolic pathways may result in unanticipated metabolic and nonmetabolic side effects, as energy homeostasis is intimately linked to an array of other cellular networks. Therefore, extensive experimentation in animal models and large, randomized, controlled multicenter clinical trials are needed to properly investigate the effects of these agents in diabetic patients.

Glucose–Insulin–Potassium

Insulin is a powerful inducer of GLUT1 and GLUT4 expression, which significantly enhance myocardial glucose uptake and utilization.¹⁹¹ Because insulin and ischemia increase GLUT4 translocation via independent but additive mechanisms, it was originally proposed that exposure to insulin during episodes of ischemia could further increase myocardial glucose uptake at the expense of FA metabolism, resulting in a lower myocardial oxygen requirement.¹⁹² However, acute administration of insulin alone (in hyperglycemic diabetics) or together with glucose and potassium (GIK) in an attempt to stimulate glucose disposal and overcome insulin resistance yielded conflicting results. The Diabetic Patients with Acute MI study showed that intensive insulin and glucose infusion during

acute myocardial infarction followed by subcutaneous insulin therapy for 3 months after myocardial infarction reduced mortality in diabetic patients.¹⁷⁹ However, the Polish GIK trial did not demonstrate any decrease in cardiovascular mortality with GIK,^{180,181} and a follow-up study (Diabetic Patients with Acute MI 2) failed to show any advantage with intensive insulin therapy.¹⁸² The failure of certain GIK regimens may be because of differential effects on glycolysis versus glucose oxidation, as GIK disproportionately stimulates glycolysis, leading to intracellular acidosis.¹⁸³ In addition, infusion of glucose into diabetic patients may further exacerbate hyperglycemia, resulting in cardiomyocyte apoptosis and oxidative stress.^{193,194} Therefore, the differences in clinical outcomes with GIK therapy may be a result of the dosage and timing of GIK administration, the patient population studied, and the negative effects of hyperglycemia.

Nicotinic Acid

Another indirect therapeutic approach to modulate FA oxidation in the failing heart is to reduce the circulating levels of FAs. Nicotinic acid and its derivatives such as acipimox reduce the activity of lipoprotein lipase in adipose tissue, which progressively decreases plasma levels of FAs, resulting in decreased myocardial FA oxidation.^{195,196} Acipimox administration in Zucker diabetic rats decreased plasma free FA, glucose, and insulin concentrations and improved glucose tolerance.¹⁹⁷ Although acute treatment with acipimox lowered plasma free FAs, reduced myocardial free FA uptake,

Table 2. Compounds Targeting Fatty Acid Metabolism as a Treatment for Diabetic Cardiomyopathy

Approach	Class	Examples	Mechanism of Action	References for Human Trials
Direct	Fatty acid (FA) uptake inhibitors	Etomoxir Perhexiline	Irreversible inhibition of CPT1 Reversible inhibition of CPT1	165,166 167–170
	Malonyl-CoA decarboxylase (MCD) inhibitors	CBM-301106	Allosteric inhibition of CPT1 by increasing malonyl-CoA	None
	Mitochondrial β -oxidation partial inhibitors	Trimetazidine Ranolazine	Inhibition of 3-ketoacyl-CoA thiolase (3-KAT) Inhibition of late sodium current, partial inhibition of FA oxidation	171–175 176,177
	Pyruvate dehydrogenase kinase (PDK) inhibitors	Dichloroacetate	Inhibition of a negative regulator of glucose oxidation	178
Indirect	Glucose–insulin–potassium (GIK)	GIK therapy	Increase glucose uptake, decrease circulating plasma free FA (FFA) levels	179–183
	Nicotinic acid	Acipimox	Decrease circulating plasma FFA levels through reduction in lipoprotein lipase (LPL)	184,185
	Glucagon-like peptide (GLP)–1 agonists	Liraglutide	Increase insulin secretion, decrease glucagon release, delay gastric emptying	186
	β -adrenoreceptor antagonists (β -blocker)	Carvedilol	Decrease circulating plasma FFAs, inhibit mitochondrial FA uptake	187–190

and enhanced glucose uptake in patients with dilated cardiomyopathy, these results were also surprisingly associated with decreased left ventricular stroke work and mechanical efficiency (work done/oxygen consumption).¹⁸⁴ This may be explained by insufficient increase in glucose uptake to compensate for the loss of FAs as a substrate, suggesting that FAs are a critical source of energy that can lead to functional disorders if inhibited by aggressive pharmacological treatment. Unfortunately, this study did not include a control group or placebo. A more recent study in patients with ischemic heart failure treated with either acipimox or placebo for 28 days demonstrated no beneficial effect of acipimox on cardiac function, despite a significant decrease in plasma FA levels.¹⁸⁵ Taken together, the available evidence suggests that FA lowering by suppression of lipolysis in adipose tissue does not improve cardiac function in heart failure.

GLP-1 Agonists

GLP-1 is a major incretin hormone released from L cells in the gut in response to food intake to stimulate insulin secretion and reduce glucagon release, leading to a reduction in blood glucose levels.¹⁹⁸ GLP-1 receptor agonists are currently used in T2DM patients who are refractory to oral hypoglycemic agents and have been shown to increase insulin synthesis and secretion, suppress glucagon secretion, and slow gastric emptying.^{199,200} Recent reports have also demonstrated that GLP-1 therapeutics have beneficial effects on the cardiovascular system; for example, the GLP-1 analogue liraglutide improves cardiac function in *db/db* mice and streptozotocin-induced diabetic rats via downregulation of endoplasmic reticulum stress.^{201,202} In addition, GLP-1 reduced intestinal lymph flow, TG absorption, and the synthesis of chylomicron-related apolipoproteins in rats.²⁰³ In the LEAD-6 trial, liraglutide reduced plasma TG and free FAs in patients with T2DM.¹⁸⁶ In addition to their therapeutic effects on diabetic cardiomyopathy, GLP-1 receptor agonists have also been shown to reduce infarct size after coronary ligation in murine models and improve the left ventricular ejection fraction in patients with heart failure.^{204–207}

β-Adrenoceptor Antagonists

β-Adrenoceptor antagonists (β-blockers) are an established, commonly prescribed treatment for improving the symptoms of angina and as a therapy for patients with ischemic heart disease. Despite concerns of masking hypoglycemic symptoms and aggravating peripheral artery disease, β-blockers are effective for the treatment of hypertension and angina in diabetic patients.²⁰⁸ Although their predominant mode of action is to reduce cardiac workload through both negative inotropic and negative chronotropic effects, some of their

beneficial effects may also be through metabolic modulation.²⁰⁹ Although short-term stimulation of β-adrenergic receptors increases glucose uptake, glycolysis, and glucose oxidation, long-term stimulation antagonizes the actions of insulin, promotes lipolysis, and increases circulating free FA levels, all of which can exacerbate insulin resistance.²¹⁰ By inhibiting catecholamine-induced lipolysis, β-blockers may reduce the mobilization of free FAs from adipose tissue and therefore decrease circulating plasma free FA concentrations.²¹¹

Long-term therapy with the β-blockers metoprolol and carvedilol is known to improve cardiac function and survival in patients with heart failure through several mechanisms, including an energy-sparing effect, consistent with the possibility of a switch in myocardial substrate preference from FA to carbohydrate oxidation.^{187–189} Using radioactive free FA and glucose tracers, heart failure patients with carvedilol treatment were found to exhibit a 57% reduction in myocardial free FA uptake.¹⁸⁸ Although this study did not note an increase in myocardial uptake of labeled glucose tracers or in the rate of glucose utilization, the decreased ratio of myocardial free FA-to-glucose utilization does suggest a “metabolic shift” induced by carvedilol. It is also important to note that there are differences in the pharmacological effects and clinical efficacy of various β-adrenergic receptor antagonists, as seen in clinical studies demonstrating that administration of carvedilol increased insulin sensitivity and improved glycemic control compared with metoprolol in patients with hypertension and T2DM.¹⁹⁰

Inhibitors of Mitochondrial FA Uptake

Several studies have suggested that direct inhibition of mitochondrial fatty acyl CoA uptake is an effective approach to shift myocardial energy metabolism from free FA to glucose utilization.^{212–214} Several CPT1 inhibitors have been studied for this purpose, including etomoxir and perhexiline. Originally introduced as an antidiabetic agent because of its hypoglycemic effects, etomoxir is an irreversible inhibitor of CPT1 that efficaciously inhibits myocardial FA oxidation and causes reciprocal activation of the PDH complex and glucose oxidation.^{215–217} Furthermore, chronic treatment with etomoxir was shown to induce the expression of the sarcoendoplasmic calcium ATPase (SERCA) in cardiomyocytes, which may lead to improved calcium handling and improved cardiac function.²¹⁸ Streptozotocin-induced diabetic rats treated with etomoxir demonstrated increased myocardial glucose oxidation rates and restoration of cardiac function.²¹⁹ Consistent with these animal data, a small open-label, uncontrolled study of etomoxir appeared to improve myocardial function and clinical status in patients with heart failure.¹⁶⁵ However, this study was not able to assess the long-term effects of etomoxir

treatment. The more recent Etoximir for the Recovery of Glucose Oxidation randomized placebo-controlled study had to be stopped prematurely because several patients with moderate heart failure in the etomoxir group developed abnormalities in liver function tests.¹⁶⁶ Although the study did not detect significant improvement in the etomoxir group compared with placebo, there was a trend toward an increase in exercise time.

Perhexiline shifts myocardial substrate utilization from FAs to carbohydrates through reversible inhibition of CPT1 and, to a lesser extent, CPT2.²¹³ Perhexiline was originally designated as a calcium channel blocker and was introduced as an anti-ischemic agent for the treatment of angina in the 1970s; however, its use declined rapidly in the 1980s amid reports of hepatic toxicity and peripheral neuropathy.¹⁶⁷ Subsequent studies demonstrated that the toxicity occurred because of chronic exposure to high drug levels, leading to phospholipidosis in the liver and peripheral nerves.¹⁶⁸ These adverse effects were found to occur most commonly in patients who are “slow hydroxylators,” bearers of a genetic variant in the P450 2D6 enzyme that is responsible for perhexiline clearance by the liver.¹⁶⁹ In vitro studies have shown that perhexiline is more effective at inhibiting the cardiac isoform of CPT1 than the liver isoform, which allows for the use of a lower dose to minimize adverse effects.²²⁰ Maintaining plasma perhexiline concentration within the therapeutic range of 150 to 600 µg/L prevents the development of long-term toxicity without compromising drug efficacy.¹⁷⁰ This has led to a resurgence of the use of perhexiline for the treatment of chronic stable angina in Australia and some parts of Asia, although it is not yet clinically available in the United States or Europe.²²¹

MCD Inhibitors

Malonyl-CoA decarboxylase (MCD) enzyme promotes FA oxidation by catalyzing the degradation of malonyl-CoA to acetyl-CoA and thus removing allosteric inhibition of CPT1 by malonyl-CoA. Cardiac overexpression of MCD protein has been observed in streptozotocin-induced diabetic rats, contributing to the high rate of FA oxidation in these animals.²²² Selective MCD inhibitors are effective at increasing myocardial levels of malonyl-CoA, leading to a decrease in cardiac FA oxidation with a parallel increase in cardiac glucose oxidation secondary to inhibition of CPT1.²²³ Animal studies using MCD inhibitors have shown that the drug is associated with reduced FA β -oxidation, increased glucose oxidation, and increased insulin sensitivity.^{224,225} In addition, MCD-deficient mice have enhanced cardiac function and efficiency, suggesting that the inhibition of malonyl-CoA may be an effective method to modulate myocardial metabolism in diabetics with heart disease.²²⁶

Partial Inhibition of Mitochondrial FA β -Oxidation

Trimetazidine is a metabolic agent used for antianginal therapy throughout Europe and Asia.²²⁷ By acting as a competitive inhibitor of 3-ketoacyl-CoA thiolase, the terminal enzyme of β -oxidation, trimetazidine shifts the energy substrate preference from FA oxidation to glucose oxidation.²²⁸ The improved coupling of glycolysis and glucose oxidation limits the intracellular acidosis attributed to glucose metabolism and also minimizes sodium and potassium overload during ischemia and reperfusion.^{229,230} This allows trimetazidine to increase cardiac efficiency during ischemic episodes by sparing ATP hydrolysis from being used to correct myocardial ionic homeostasis. The effects of trimetazidine in experimental studies make this drug an attractive treatment for angina in diabetic patients.¹⁷¹ This hypothesis was confirmed by the TRIMPOL-1 trial, in which the addition of trimetazidine to the treatment regimen improved exercise capacity and duration and reduced anginal attacks in diabetic patients with chronic stable angina without influencing heart rate or blood pressure.¹⁷² Subsequent studies have also shown trimetazidine to improve heart function and overall insulin sensitivity in patients with idiopathic dilated cardiomyopathy.^{173,174} However, reports of side effects, such as parkinsonian symptoms and restless leg syndrome, have recently prompted the European Medicines Agency to restrict use of trimetazidine-containing medicine in the treatment of patients with angina to second-line, add-on therapy and to discontinue its use in patients who develop movement disorders.¹⁷⁵

Ranolazine is an antianginal drug used in the United States and some European countries for the treatment of chronic stable angina, with the additional benefit of glycemic control.^{231,232} Similar to trimetazidine, ranolazine have been shown to suppress FA oxidation in rat cardiac and skeletal muscle and result in a reciprocal increase in glucose oxidation.²³³ Recent reports also implicate the ability of ranolazine to inhibit the late inward sodium channel, which prevents adverse increases in sodium-triggered calcium overload that occur in failing cardiomyocytes.²³⁴ The MARISA (Monotherapy Assessment of Ranolazine in Stable Angina) and CARISA (Combination Assessment of Ranolazine in Stable Angina) clinical trials demonstrated that ranolazine is an effective antianginal therapy, alone or in combination with other antianginal agents, by increasing the time to 1-mm ST-segment depression, reducing the number of angina attacks, and reducing nitroglycerin consumption in both diabetic and nondiabetic patients.^{176,177} Subgroup analysis of the CARISA trial also showed significant reduction of hemoglobin A1c in diabetic patients treated with ranolazine, consistent with increased systemic glucose clearance. Ranolazine also decreased the incidence of ventricular tachycardia, supraventricular

tricular tachycardia, and ventricular pauses, likely because of its ability to inhibit the late sodium current.^{235,236} Therefore, ranolazine may be particularly effective in treating heart disease in diabetic patients.

Reduction in FA-Induced Inhibition of Glucose Oxidation

Dichloroacetate (DCA) promotes myocardial glucose oxidation at the expense of FA oxidation by inhibiting the major negative regulator of glucose oxidation, PDK.²³⁷ The PDH complex is normally in its active dephosphorylated state to facilitate glucose oxidation by directing pyruvate into the tricarboxylic acid cycle. The main mechanism of long-term PDH complex inactivation is its phosphorylation by PDK. Therefore, by inhibiting PDK, DCA increases glucose oxidation. In perfused working rat hearts, DCA enhanced postischemic recovery of cardiac function by improving the coupling between glycolysis and glucose oxidation.²³⁸ In addition, DCA restored contractile performance in cardiomyocytes isolated from streptozotocin-induced diabetic rats.²³⁹ Another PDK inhibitor, SDZ048-619, increased PDH complex activity in the liver, kidney, and skeletal and cardiac muscle of Zucker diabetic rats; however, it did not lower blood glucose.²⁴⁰ Although clinical experience with DCA is limited, DCA increased left ventricular stroke volume and myocardial efficiency in 9 patients with coronary artery disease.¹⁷⁸ Further animal and human studies are needed to better characterize the safety profile of PDK inhibitors and their relevance in the treatment of cardiac dysfunction in diabetic patients.

Conclusions

Despite considerable research efforts, we are yet to uncover the precise mechanism by which molecular changes in cardiac metabolism are linked to the gross pathology of the diabetic heart. However, the major contribution of metabolic inflexibility to this process is becoming well recognized,⁵³ and the model for the development of diabetic cardiomyopathy is emerging. The inciting event appears to be the increased reliance of the heart on lipid substrates. This may be a result to reduced glucose availability, as found in T1DM, or increased availability of FA in circulation in metabolic syndrome and T2DM. Elevated levels of free FAs inside the cardiomyocyte, while providing ample substrate for ATP generation, also directly and indirectly affect multiple signaling pathways, including inhibition of insulin signaling, suppression of glycolysis, and activation of the PPAR α transcription factor, all of which lock the heart in a metabolically rigid state. The diabetic heart thus can no longer sufficiently increase its glucose utilization in response

to elevated workload requirements, making it more vulnerable to external insults. Moreover, oxidation of fat brings about myriad other maladaptive changes, including reduced efficiency of ATP production and export, generation of toxic FA intermediates, and accumulation of lipids inside the myocardium. As a consequence of these changes, cardiac function gradually declines, finally manifesting itself as diabetic cardiomyopathy. The therapeutic strategies to reverse diabetic cardiomyopathy thus must be aimed at restoring the lipid–glucose balance and preventing metabolic lockdown of the diabetic heart.

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