

# Diabetes and ischemia: similarities in cardiac energy metabolism

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## Abstract

Ischemic heart disease (IHD) and diabetes mellitus (DM) are leading causes of death worldwide. Cardiac energy metabolism is profoundly altered in both of these conditions, which can lead to permanent cardiac pathologies that include heart failure and diabetic cardiomyopathy. Diabetic hearts show an increased dependence on oxidation of fatty acids for the production of adenosine triphosphate (ATP) accompanied by an impairment of glucose oxidation. Such features resemble to a large extent the metabolic phenotype of the ischemic heart during ischemia and reperfusion. Likewise, ischemic myocardium displays the insulin insensitivity that typically exists in the diabetic heart. Other common features include reduced circulating levels of adiponectin, a cardioprotective adipokine, and an enhanced state of acetylation of specific lysine residues in enzymes and transcription factors that are essential in energy metabolic processes. Recognizing cardiac metabolism similarities between DM and IHD should help to devise and optimize metabolic modulatory therapies for comorbidity patients. ■ *Heart Metab.* 2015;68:4-8

**Keywords:** cardiac efficiency; diabetes; energy metabolism; heart; ischemia

Under normal aerobic conditions, fatty acid oxidation contributes around 70% of cardiac energy production, with the remainder being mainly provided by the oxidation of glucose.<sup>1</sup> Fatty acids and glucose compete at several regulatory points and although fatty acid oxidation has a greater potential to produce adenosine triphosphate (ATP) compared with glucose, this comes at the expense of using more oxygen.<sup>2</sup> In addition to the lower ATP/oxygen ratio, other mechanisms—such as mitochondrial fatty acid uncoupling and futile fatty acid cycling into and from triacylglycerol (TAG) stores—contribute to a decreased efficiency of fatty acids as energy substrates compared with glucose. As such, a greater reliance on the oxidation of fatty acids can decrease cardiac efficiency, especially un-

der conditions of limited oxygen supply or increased workloads.<sup>1</sup>

Cardiac energy metabolism is markedly altered in both ischemic heart disease (IHD) and diabetes mellitus (DM).<sup>1</sup> Such metabolic derangements contribute to the severity of cardiac disease. In IHD, alterations in cardiac energy metabolism contribute to the severity of the ischemic injury, whereas in DM, they can play a role in the pathophysiology of diabetic cardiomyopathy (a myocardial pathology occurring in DM that predisposes the patients to heart failure independent of vascular factors).<sup>3</sup> In both the diabetic and ischemic heart, there is an increased reliance on mitochondrial oxidation of fatty acids compared with carbohydrates, which contributes to cardiac inefficiency and contractile dysfunction.<sup>1,3</sup> As a result, modulation

## Abbreviations

**ACC:** acetyl-Coenzyme A carboxylase; **DM:** diabetes mellitus; **I/R:** ischemia/reperfusion; **IHD:** ischemic heart disease; **MCD:** malonyl-Coenzyme A decarboxylase; **MI:** myocardial infarction; **PDH:** pyruvate dehydrogenase

of cardiac energy metabolism to directly or indirectly increase glucose oxidation and/or decrease fatty acid oxidation can improve heart function in IHD and DM.<sup>1</sup> This review will focus on the similarities between metabolic profiles of ischemic and diabetic hearts, as well as metabolic modulatory approaches that are potentially beneficial.

## Energy metabolism in ischemia/reperfusion injury

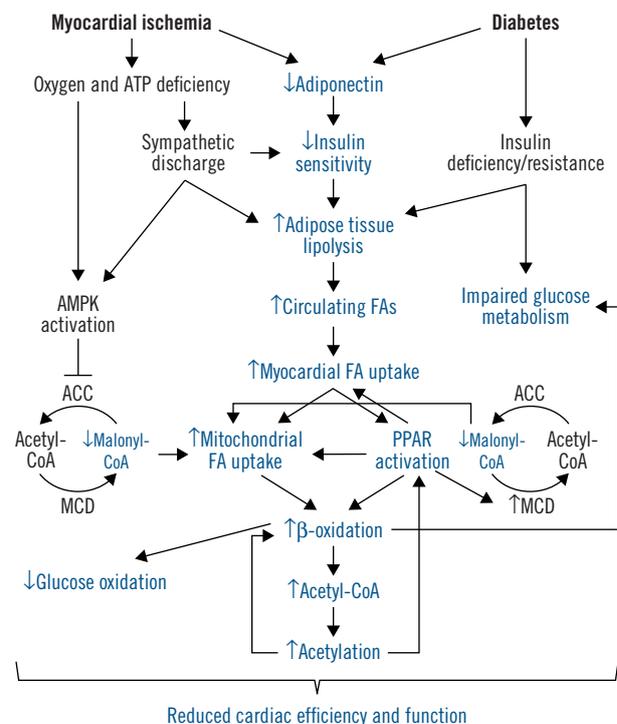
Alterations in myocardial energy metabolism during and after ischemia occur in response to acute changes in oxygen availability, as well as to changes in the exposure of the heart to circulating energy substrates and to direct deregulation of cardiac energy production processes. Due to limitations in oxygen supply, the ischemic heart increases its reliance on anaerobic glycolysis for ATP production. Unfortunately, simultaneous reductions in glucose oxidation causes an accumulation of lactate and protons in the myocardium, thus contributing to the waste of the already depleted ATP in rectifying ionic imbalances brought about by ischemia.<sup>4</sup>

During reperfusion (eg, by thrombolysis or revascularization), fatty acid oxidation becomes the predominant energy source and significantly outmatches glucose oxidation.<sup>1,4</sup> This is mainly attributed to increased availability of circulating fatty acids accompanied by a reduced myocardial uptake of glucose secondary to sympathetic discharge, which stimulates lipolysis from adipose tissue and decreases insulin secretion and sensitivity.<sup>4</sup> Furthermore, during ischemia, the concentration of cardiac malonyl-Coenzyme A (malonyl-CoA), an inhibitor of fatty acid  $\beta$ -oxidation through its action on carnitine palmitoyltransferase I (CPT I), dramatically decreases as a result of decreased synthesis and maintained degradation (Figure 1).<sup>5</sup> The resultant increase in fatty acid oxidation inhibits glucose oxidation by depressing the activity of the rate limiting enzyme of glucose oxidation, pyruvate dehydrogenase (PDH).<sup>4</sup> This occurs while glycolysis is not proportionally sup-

pressed, leading to lactate and proton production that contributes to contractile dysfunction.<sup>1,4,5</sup>

## Energy metabolism in the diabetic heart

The diabetic heart is overly reliant on fatty acid oxidation as a source of energy, due to elevated levels of circulating fatty acids and upregulation of proteins involved in fatty acid uptake, transport, and oxidation.<sup>1</sup> While some of these alterations occur secondary to defective insulin signaling,<sup>6</sup> others are a result of local myocardial derangements.<sup>3</sup> This includes increased expression of lipoprotein lipase (which liberates free fatty acids from circulating TAG) in states of insulin resistance. Increased lipid accumulation, such as diacylglycerols (DAG), therefore occurs, which may lead to



**Fig. 1** Cardiac energy metabolism similarities in diabetes and ischemic heart disease. Diabetic and ischemic hearts share many metabolic characteristics produced by collaborating and interconnecting pathways and mechanisms. The hallmark of diabetic and ischemic/reperfused hearts is the increased metabolism of fatty acids, particularly  $\beta$ -oxidation, which in the face of impaired glucose oxidation and insulin sensitivity can lead eventually to reduced cardiac efficiency and function. Also, circulating adiponectin, a "good" adipokine, is reduced in both diseases, thus contributing to insulin resistance and cardiac dysfunction. Additionally, the lysine acetylation status of myocardial proteins is generally increased and may contribute to and result from the increased reliance on fatty acid as an energy substrate.

**Abbreviations:** ACC, acetyl-Coenzyme A carboxylase; AMPK, AMP-activated protein kinase; ATP, adenosine triphosphate; CoA, Coenzyme A; FA(s), fatty acid(s); MCD, malonyl-Coenzyme A decarboxylase; PPAR, peroxisome proliferator-activated receptors.

lipotoxicity-induced cardiac dysfunction and diabetic cardiomyopathy.<sup>7</sup> Altered regulatory processes of fatty acid  $\beta$ -oxidation also contribute to the increased fatty acid  $\beta$ -oxidation in the diabetic heart. This includes a decrease in cardiac malonyl-CoA levels, as well as upregulation of several proteins involved in fatty acid  $\beta$ -oxidation.<sup>3,8</sup> Of note, fatty acids are natural ligands of peroxisome proliferator-activated receptors (PPARs), thus increasing their activity in the fatty acid-overwhelmed diabetic myocardium.<sup>1</sup> Enhanced uptake and oxidation of fatty acids results in inhibition of glucose uptake and utilization by the heart, which are typical characteristics of DM.<sup>1,3</sup> PPAR- $\alpha$  also enhances the expression of PDH kinase 4 (PDK4), which phosphorylates and deactivates PDH. Furthermore, PPAR- $\alpha$  expression appears to indirectly correlate with the main cardiac glucose transporter, GLUT4, thus decreasing both glucose uptake and oxidation.<sup>1</sup>

### What is common between ischemia and diabetes mellitus?

Common metabolic aspects of DM and IHD include: (i) elevated levels of circulating fatty acids as a result of different, but related, hormonal perturbations, (ii) decreased myocardial malonyl-CoA levels, through distinctive processes that eventually produce a similar effect of accelerated mitochondrial uptake and oxidation of long-chain fatty acids, and (iii) a prevailing state of blunted glucose oxidation, by virtue of either temporary (eg, ischemia/reperfusion [I/R]) or long-lasting (eg, DM) insulin resistance that includes PDH inhibition.

Other similarities also exist. For example, protein acetylation, a posttranslational modification, is globally increased in I/R mouse hearts.<sup>9</sup> This is attenuated by activation of NAD<sup>+</sup>-dependent histone deacetylases,<sup>10</sup> which translates into cardioprotection. Increased acetylation is also seen in the diabetic heart.<sup>11</sup> Key mitochondrial proteins involved in fatty acid  $\beta$ -oxidation are hyperacetylated with a concomitant increase in their activities and in total fatty acid  $\beta$ -oxidation rates.<sup>12</sup>

Another shared feature is the level, and effects of, circulating adiponectin, an adipokine that plays a key role in preventing and ameliorating insulin resistance and cardiovascular dysfunction.<sup>13</sup> Circulating and cardiac levels of adiponectin and myocardial expression of cardiac adiponectin type 1 receptors are di-

minished in diabetic rats and negatively correlate with deterioration of cardiac structure and function with positive correlation to systemic glycemic control.<sup>14</sup> Interestingly, circulating adiponectin is also reduced in coronary artery patients.<sup>13</sup>

### Pharmacological therapies targeting energy metabolism in DM and IHD

A potential therapeutic approach to treating both DM and IHD involves inhibition of fatty acid oxidation, which can have beneficial effects on cardiac efficiency and function. Indeed, a number of pharmacological metabolic modulators function by tilting the balance toward cardiac glucose oxidation and away from fatty acid oxidation.

#### Glucose-insulin-potassium therapy

Glucose-insulin-potassium (GIK) therapy is an approach based on resisting ischemic injury by rectifying glucose/insulin defects that typically occur in DM. The beneficial effects of GIK therapy on cardiac infarct size and postischemic function are associated with increased rates of glycolysis and reduced levels of circulating fatty acids.<sup>15</sup> GIK was shown to reduce mortality rates post-myocardial infarction (MI) and to reduce the composite of 1-year cardiac arrest or mortality, as well as the composite of 1-year cardiac arrest, mortality, or heart failure hospitalization.<sup>15</sup> A study in diabetic MI patients showed GIK to effect a more stable cardiac index and blood potassium level, a shorter time on mechanical ventilation, less atrial fibrillation, and better glycemic control.<sup>16</sup> However, other trials failed to demonstrate GIK cardioprotection,<sup>17</sup> possibly due to potentiation of myocardial acidosis by disproportionately stimulating glycolysis compared with glucose oxidation.<sup>1</sup>

#### Trimetazidine

Trimetazidine is an anti-anginal drug that directly decreases fatty acid oxidation, thereby indirectly stimulating glucose oxidation.<sup>18</sup> It reduces angina attacks and nitrate consumption, and improves exercise tolerance.<sup>19</sup> Trimetazidine has been shown to ameliorate cardiac dysfunction in db/db diabetic mice.<sup>20</sup> It is highly recommended that trimetazidine be considered when treating diabetic patients with IHD.

### Etomoxir

Etomoxir is an irreversible inhibitor of CPT I, originally designed to treat DM.<sup>1</sup> It promotes the metabolic switch toward glucose oxidation and improves cardiac function post ischemia and in diabetic hearts, suggesting a potential benefit in diabetic cardiomyopathy.<sup>1</sup> However, although etomoxir improved the ejection fraction and cardiac output in a small clinical trial in heart failure patients, it was associated with liver toxicity, probably due to its irreversible inhibition of CPT I, which necessitated discontinuation of the study.<sup>4</sup>

### PPAR- $\gamma$ agonists

Thiazolidinediones (TZDs) are antidiabetic drugs that inhibit oxidation of fatty acids in the heart through reducing their circulating levels secondary to their effect on adipose tissue, where their target, PPAR- $\gamma$ , has the highest expression and where they increase the sequestration of fatty acids and TAG.<sup>1</sup> TZDs increase myocardial glucose uptake and oxidation and preserve postischemic cardiac function in animal models of DM.<sup>4</sup> However, the use of TZDs was reported to increase the risk of MI and exacerbate heart failure in type 2 DM patients, probably as a result of their adverse effects, eg, fluid retention and peripheral edema, lipid profile derangement, and antagonism of angiogenesis.<sup>21</sup>

### Malonyl-Coenzyme A decarboxylase inhibitors

Malonyl-Coenzyme A decarboxylase (MCD) inhibitors produce the favored metabolic shift in normal and ischemic hearts and potentiate insulin sensitivity secondary to elevating myocardial malonyl-CoA levels and CPT I inhibition.<sup>22</sup> MCD inhibitors are cardioprotective against ischemia and control blood glucose concentration in rodents.<sup>4</sup>

### Conclusion

IHD and DM share a number of energy metabolism similarities. Several biochemical and pathophysiological features converge to increase the reliance on fatty acid  $\beta$ -oxidation, accompanied by deregulated insulin and adipokine actions that favor a state of compromised cardiac efficiency, structure, and function. It is

therefore important to identify the major similarities and differences among cardiac metabolic syndromes in order to devise therapeutic interventions aiming to improve cardiac health. ■

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