

# Cardiac energy metabolism in diabetes

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## Abstract

Diabetes is a significant risk factor for cardiovascular disease, and ongoing efforts aim to elucidate how diabetes precipitates ventricular dysfunction. Myocardial energy metabolism is intricately regulated because the heart—the most metabolically demanding organ in the body on a per gram basis—must dynamically metabolize a diverse range of fuel sources. However, in type 1 and type 2 diabetes mellitus, increases in myocardial fatty acid oxidation and decreases in myocardial glucose oxidation are observed, and it has been postulated that these metabolic perturbations are key contributors to diabetes-related ventricular dysfunction. With a number of pharmacological tools now available to modulate energy metabolism, targeting the diabetes-induced alterations in myocardial energy metabolism may be a promising strategy to improve ventricular function in diabetic subjects. Such a strategy is widely supported by current evidence in preclinical studies. ■ *Heart Metab.* 2017;73:33-36

**Keywords:** energy metabolism; fatty acid oxidation; glucose oxidation; type 1 diabetes; type 2 diabetes

## Introduction

As of 2014, it was estimated that there were over 420 million people worldwide living with diabetes, of which 90% was accounted for by type 2 diabetes mellitus (T2DM). Despite having a variety of different drug classes to control hyperglycemia in these individuals, the vast majority of diabetics will eventually die from cardiovascular causes such as myocardial infarction and heart failure (HF).<sup>1,2</sup> Hence, there has been and continues to be a strong effort within the scientific and medical community to understand the cardiovascular actions of therapies for treating diabetes, in addition to understanding how diabetes itself increases the risk of developing cardiovascular

disease. With regard to the latter, we have now come to appreciate that energy metabolism in the myocardium of an individual with type 1 diabetes mellitus (T1DM) or T2DM is significantly different from that in a healthy individual.<sup>2-5</sup> Of particular importance, the healthy heart is a metabolic omnivore with high flexibility that is able to consume a wide variety of substrates according to their availability throughout various physiological states (eg, feeding versus starvation). However, during both T1DM and T2DM, the robust increase in circulating free fatty acids and triglycerides greatly augments fatty acid delivery to the myocardium, making fat the primary fuel choice for the heart's energy demands, which severely limits its ability to adapt to and use other energy sources (*Figure 1*). The aims of this

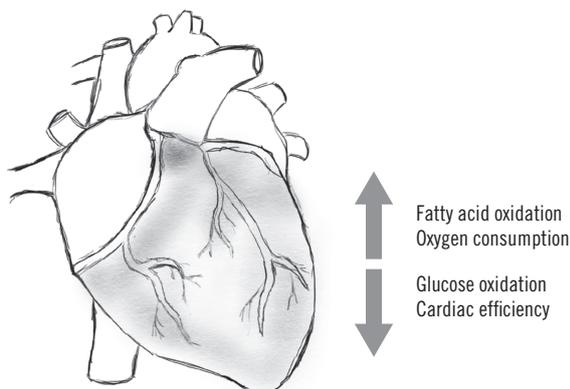
### Abbreviations

**ATP:** adenosine triphosphate; **CoA:** coenzyme A; **CPT-1:** carnitine palmitoyltransferase-1; **DCA:** dichloroacetate; **HF:** heart failure; **MRI:** magnetic resonance imaging; **PDH:** pyruvate dehydrogenase; **PET:** positron emission tomography; **T1DM:** type 1 diabetes mellitus; **T2DM:** type 2 diabetes mellitus

refresher article are to highlight the specific myocardial metabolic alterations observed in patients with T1DM and T2DM, and to describe whether these metabolic alterations can be targeted to improve cardiac function in diabetic subjects.

### Myocardial energy metabolism in type 1 diabetes

Because T1DM is often the result of insulin deficiency, many of the alterations in myocardial energy metabolism in a T1DM individual can be attributed to deficient myocardial insulin action. In a healthy insulin-sensitive individual, insulin acts to increase glucose uptake in the heart, leading to increases in both glycolysis and glucose oxidation.<sup>6</sup> Increases in glucose oxidation lead to a corresponding reduction in fatty acid oxidation, a phenomenon first described by Shipp and colleagues<sup>7</sup> in the 1960s, but later given prominence by Phillip Randle and colleagues. As such, this reciprocal glucose–fatty acid relationship for oxidative metabolism is commonly referred to as the “Randle Cycle.”<sup>8</sup> Insulin also decreases myocardial fatty acid oxidation rates indirectly by inhibiting adipose tissue lipolysis. In addition,



**Fig. 1** Alterations in myocardial energy metabolism in the diabetic heart. The figure illustrates the prominent metabolic perturbations that take place in the heart during diabetes, which are characterized by an increase in fatty acid oxidation rates and subsequent decrease in glucose oxidation rates. These changes in oxidative metabolism are associated with an increase in myocardial oxygen consumption, which contributes to a reduction in cardiac efficiency.

insulin directly inhibits myocardial fatty acid oxidation rates by activating acetyl coenzyme A (CoA) carboxylase to increase levels of malonyl CoA, a potent endogenous inhibitor of carnitine palmitoyltransferase-1 (CPT-1), which subsequently inhibits mitochondrial fatty acid uptake.<sup>3</sup> Therefore, in a T1DM individual, myocardial fatty acid oxidation rates are markedly elevated as a result of absent insulin action, whereas glucose oxidation and glycolysis rates are severely diminished. Indeed, studies in rats subjected to experimental T1DM via tail-vein injection of streptozotocin (55 mg/kg) demonstrate that fatty acid oxidation accounts for approximately 95% of total oxidative adenosine triphosphate (ATP) production during isolated aerobic working heart perfusion.<sup>9</sup> Likewise, the Akita mouse (a mouse model of T1DM due to genetic mutation in the insulin 2 [*Ins2*] gene) demonstrates no changes in glucose oxidation and significant increases in myocardial fatty acid oxidation during isolated aerobic working heart perfusion,<sup>10</sup> though the changes in fatty acid oxidation are not nearly as prominent as those seen in the streptozotocin model of T1DM. Similar findings have been recapitulated in humans, in which positron emission tomography (PET) imaging studies in T1DM subjects with 1-<sup>11</sup>C-glucose and 1-<sup>11</sup>C-palmitate revealed reductions in myocardial glucose utilization rates and increases in myocardial fatty acid oxidation rates, respectively.<sup>11</sup>

### Myocardial energy metabolism in type 2 diabetes

The myocardial metabolic alterations reported in animal models of obesity and/or T2DM, or in T2DM patients are similar to those observed in a T1DM individual. In mice subjected to chronic high-fat feeding (60% kcal from lard) for 12 weeks to induce experimental obesity, marked reductions in glucose oxidation rates are observed, whereas fatty acid oxidation rates remain largely unaffected.<sup>12</sup> Of interest, severe insulin resistance is observed in this model with regard to insulin's ability to promote glucose oxidation, such that in the presence of insulin, the vast majority of oxidative energy metabolism is met through the oxidation of fatty acids.<sup>12</sup> In genetic mouse models of T2DM, including both leptin-deficient *ob/ob* and leptin receptor-deficient *db/db* mice, marked increases in myocardial fatty acid oxidation and corresponding decreases in glucose oxidation rates are observed during isolated aerobic working heart perfusions.<sup>13</sup> These changes in myocardial energy metabolism are associated with sig-

nificant increases in myocardial oxygen consumption rates, but are not matched by an equivalent increase in cardiac work/power, such that the efficiency of contractile function is reduced in both *ob/ob* and *db/db* mice.<sup>13</sup> These observations have been recapitulated in a human cohort study of obese women from Petersen and colleagues, whereby PET imaging studies revealed marked increases in fatty acid oxidation rates in obese women, which strongly correlated with the degree of glucose intolerance.<sup>14</sup> Moreover, increasing obesity is inversely associated with cardiac efficiency in these women.<sup>14</sup> Additional PET imaging studies have recorded similar observations, as Rijzewijk and colleagues demonstrated an elevation in myocardial fatty acid oxidation rates and a decline in myocardial glucose uptake in T2DM patients with diastolic dysfunction.<sup>15</sup>

### Myocardial energy metabolism alterations in diabetic subjects with heart failure

An important potential confounding factor when assessing the impact of diabetes on myocardial energy metabolism is the comorbidity of HF. Diabetes is a major risk factor for HF, and it is estimated that 30% to 40% of HF patients have some form of diabetes.<sup>16</sup> Because HF is associated with its own distinct myocardial metabolic phenotype, most notably a reduction in fatty acid oxidation rates that appears to correlate with the severity of the decline in ventricular function,<sup>3,5</sup> careful consideration needs to be taken with interpretation of myocardial energy metabolism profiles in comorbid diabetic/HF individuals.

### Optimizing myocardial energy metabolism to improve cardiac function in diabetes

A key question arising from the myocardial metabolic aberrations in diabetic subjects is whether they can be targeted to improve cardiac function in these individuals. Of particular relevance, a number of studies in animal models of obesity and/or diabetes have demonstrated that pharmacological activation of glucose oxidation often improves both cardiac function and contractile efficiency of the heart.<sup>2,3</sup> For example, isolated working hearts from rats treated with streptozotocin to induce T1DM demonstrate a marked reduction in cardiac function during aerobic perfusion, which is negated by the inclusion of 0.5 mM dichloroacetate (DCA) in the perfusate.<sup>17</sup> DCA is a pharmacological in-

hibitor of pyruvate dehydrogenase (PDH) kinase, and thereby increases glucose oxidation by preventing phosphorylation-induced inhibition of PDH, the rate-limiting enzyme of glucose oxidation.<sup>18</sup> Likewise, DCA supplementation in the drinking water (final concentration of 1 mM) has also been shown to increase myocardial glucose oxidation rates via a novel <sup>13</sup>C hyperpolarized magnetic resonance imaging (MRI) method in a rat model of experimental T2DM (long-term high-fat feeding plus a single low-dose streptozotocin injection), ultimately resulting in an abrogation of diastolic dysfunction.<sup>19</sup> Of interest, inhibiting fatty acid oxidation rates in animal models of experimental obesity/insulin resistance also has beneficial actions on the myocardium. Indeed, mice with a deficiency for malonyl CoA decarboxylase, which decreases fatty acid oxidation rates due to elevating levels of malonyl CoA and subsequent inhibition of CPT-1, demonstrate increases in cardiac efficiency, as well as a marked improvement in insulin-stimulated glucose oxidation rates.<sup>12</sup> In addition, the antianginal agent trimetazidine, which reduces myocardial fatty acid oxidation rates by inhibiting the  $\beta$ -oxidation enzyme, 3-ketoacyl-CoA thiolase, can attenuate diastolic dysfunction in middle-aged mice subjected to experimental obesity/insulin resistance.<sup>20</sup> Similarly, trimetazidine treatment for 6 months in T2DM subjects with idiopathic cardiomyopathy improves both diastolic function and systolic function.<sup>21</sup>

As mentioned in the previous section, myocardial fatty acid oxidation rates are often impaired in individuals with HF<sup>3,5</sup>; thus, it may be anticipated that inhibiting myocardial fatty acid oxidation in a comorbid diabetic/HF subject would be undesirable. Nevertheless, treatment with trimetazidine for 3 months has been shown to reduce myocardial fatty acid oxidation rates and improve ventricular function in systolic HF patients with idiopathic dilated cardiomyopathy.<sup>22</sup> Moreover, treatment of optimally medicated chronic HF patients for 8 weeks with perhexiline, a fatty acid oxidation inhibitor that directly antagonizes CPT-1, also leads to significant improvements in ventricular function.<sup>23</sup> Therefore, inhibition of myocardial fatty acid oxidation rates may still be potentially beneficial even in a comorbid diabetic/HF subject.

### Summary

It has been strongly established that both T1DM and T2DM lead to significant alterations in myocardial en-

ergy metabolism, most notably an elevation in fatty acid oxidation rates and a reduction in glucose oxidation rates (Figure 1), as determined in preclinical studies. Elevations in myocardial fatty acid oxidation have also been seen in human subjects with T1DM or T2DM, but because methodologies to assess glucose oxidation in vivo are limited, confirmation that glucose oxidation rates are reduced in diabetic patients is lacking. However, the development of the novel  $^{13}\text{C}$  hyperpolarized MRI method to quantify glucose oxidation in vivo has recently been successfully applied to human subjects,<sup>24</sup> suggesting that we may soon have confirmation of reduced myocardial glucose oxidation rates in diabetic subjects. Current evidence from preclinical studies supports the notion that normalizing diabetes-induced alterations in myocardial energy metabolism may be a novel approach to attenuate diabetes-induced ventricular dysfunction. Though human data is lacking, this is a promising area that requires further investigation. ■

## REFERENCES

1. Ussher JR, Sutendra G, Jaswal JS. The impact of current and novel anti-diabetic therapies on cardiovascular risk. *Future Cardiol.* 2012;8:895-912.
2. Zlobine I, Gopal K, Ussher JR. Lipotoxicity in obesity and diabetes-related cardiac dysfunction. *Biochim Biophys Acta.* 2016;1860:1555-1568.
3. Lopaschuk GD, Ussher JR, Folmes CD, Jaswal JS, Stanley WC. Myocardial fatty acid metabolism in health and disease. *Physiol Rev.* 2010;90:207-258.
4. Ussher JR. The role of cardiac lipotoxicity in the pathogenesis of diabetic cardiomyopathy. *Expert Rev Cardiovasc Ther.* 2014;12:345-358.
5. Ussher JR, Elmariah S, Gerszten RE, Dyck JR. The Emerging role of metabolomics in the diagnosis and prognosis of cardiovascular disease. *J Am Coll Cardiol.* 2016;68:2850-2870.
6. Brownsey RW, Boone AN, Allard MF. Actions of insulin on the mammalian heart: metabolism, pathology and biochemical mechanisms. *Cardiovasc Res.* 1997;34:3-24.
7. Shipp JC, Opie LH, Challoner D. Fatty acid and glucose metabolism in the perfused heart. *Nature.* 1961;189:1018-1019.
8. Randle PJ, Garland PB, Hales CN, Newsholme EA. The glucose fatty-acid cycle. Its role in insulin sensitivity and the metabolic disturbances of diabetes mellitus. *Lancet.* 1963;1:785-789.
9. Sakamoto J, Barr RL, Kavanagh KM, Lopaschuk GD. Contribution of malonyl-CoA decarboxylase to the high fatty acid oxidation rates seen in the diabetic heart. *Am J Physiol Heart Circ Physiol.* 2000;278:H1196-H1204.
10. Basu R, Oudit GY, Wang X, et al. Type 1 diabetic cardiomyopathy in the Akita (Ins2WT/C96Y) mouse model is characterized by lipotoxicity and diastolic dysfunction with preserved systolic function. *Am J Physiol Heart Circ Physiol.* 2009;297:H2096-H2108.
11. Herrero P, Peterson LR, McGill JB, et al. Increased myocardial fatty acid metabolism in patients with type 1 diabetes mellitus. *J Am Coll Cardiol.* 2006;47:598-604.
12. Ussher JR, Koves TR, Jaswal JS, et al. Insulin-stimulated cardiac glucose oxidation is increased in high-fat diet-induced obese mice lacking malonyl CoA decarboxylase. *Diabetes.* 2009;58:1766-1775.
13. Buchanan J, Mazumder PK, Hu P, et al. Reduced cardiac efficiency and altered substrate metabolism precedes the onset of hyperglycemia and contractile dysfunction in two mouse models of insulin resistance and obesity. *Endocrinology.* 2005;146:5341-5349.
14. Peterson LR, Herrero P, Schechtman KB, et al. Effect of obesity and insulin resistance on myocardial substrate metabolism and efficiency in young women. *Circulation.* 2004;109:2191-2196.
15. Rijzewijk LJ, van der Meer RW, Lamb HJ, et al. Altered myocardial substrate metabolism and decreased diastolic function in nonischemic human diabetic cardiomyopathy: studies with cardiac positron emission tomography and magnetic resonance imaging. *J Am Coll Cardiol.* 2009;54:1524-1532.
16. Dei Cas A, Fonarow GC, Gheorghide M, Butler J. Concomitant diabetes mellitus and heart failure. *Curr Probl Cardiol.* 2015;40:7-43.
17. Nicholl TA, Lopaschuk GD, McNeill JH. Effects of free fatty acids and dichloroacetate on isolated working diabetic rat heart. *Am J Physiol.* 1991;261:H1053-H1059.
18. Ussher JR, Wang W, Gandhi M, et al. Stimulation of glucose oxidation protects against acute myocardial infarction and reperfusion injury. *Cardiovasc Res.* 2012;94:359-369.
19. Le Page LM, Rider OJ, Lewis AJ, et al. Increasing pyruvate dehydrogenase flux as a treatment for diabetic cardiomyopathy: a combined  $^{13}\text{C}$  hyperpolarized magnetic resonance and echocardiography study. *Diabetes.* 2015;64:2735-2743.
20. Ussher JR, Fillmore N, Keung W, et al. Trimetazidine therapy prevents obesity-induced cardiomyopathy in mice. *Can J Cardiol.* 2014;30:940-944.
21. Zhao P, Zhang J, Yin XG, et al. The effect of trimetazidine on cardiac function in diabetic patients with idiopathic dilated cardiomyopathy. *Life Sci.* 2013;92:633-638.
22. Tuunanen H, Engblom E, Naum A, et al. Trimetazidine, a metabolic modulator, has cardiac and extracardiac benefits in idiopathic dilated cardiomyopathy. *Circulation.* 2008;118:1250-1258.
23. Lee L, Campbell R, Scheuermann-Freestone M, et al. Metabolic modulation with perhexiline in chronic heart failure: a randomized, controlled trial of short-term use of a novel treatment. *Circulation.* 2005;112:3280-3288.
24. Cunningham CH, Lau JY, Chen AP, et al. Hyperpolarized  $^{13}\text{C}$  metabolic MRI of the human heart: initial experience. *Circ Res.* 2016;119:1177-1182.