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Energy metabolic changes in the diabetic heart

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Abstract

The progression of the metabolic syndrome to diabetes is accompanied by dramatic changes in cardiac energy metabolism. This includes an increased reliance of the heart on fatty acids as a source of energy, and a decrease in glucose metabolism. These metabolic alterations can contribute to the development of diabetic cardiomyopathies. Therapeutic strategies that inhibit fatty acid oxidation or stimulate glucose metabolism are potential approaches that can prevent the development of cardiac dysfunction during the development of diabetes. This paper discusses the metabolic changes that occur in diabetes, and the potential approaches that can be used to treat diabetic cardiomyopathies.

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Keywords: Fatty acid oxidation; hyperglycemia; insulin resistance; metabolic syndrome.

Introduction

The heart relies almost exclusively on aerobic oxidation of substrates in order to generate ATP, which is required to maintain its cellular and contractile functions. A keen interest in the substrate supply in human heart failure (HF) dates back more than 50 years to the pioneering work of Bing and colleagues [1]. Both glucose and free fatty acids (FFAs) are major physiological fuels for the normal myocardium; glucose in the fed state and FFAs in the fasted state. Glucose uptake is promoted by insulin and inhibited by high concentrations of FFAs [2, 3], both of which occur in type 2 diabetes mellitus (T2DM). Such diabetes commonly occurs against a background of the metabolic syndrome, which in turn predisposes to cardiovascular abnormalities. The key to understanding the metabolism of T2DM lies in the 2-fold aspects of insulin resistance, which has metabolic consequences by promoting hyperglycemia and has pro-inflammatory effects. This paper will concentrate on the adverse metabolic effects of hyperglycemia, the metabolic syndrome, and the diabetic heart. Similar principles apply to the ischemic and failing heart [4], showing how robust these metabolic principles are.

Metabolic syndrome and progression to diabetes

The metabolic syndrome

When this state is fully developed, there are five features: an increased waistline, fasting hyperglycemia, blood pressure (BP) elevation, increased circulating triglycerides and decreased circulating high-density lipoprotein (HDL) cholesterol [5]. Three of these are required for the diagnosis of the metabolic syndrome [6] (*Figure 1*). The metabolic syndrome comprises a group of cardiovascular risk factors each of which individually may only be only of borderline

Abbreviations

AMPK: AMP-activated protein kinase; **BP:** blood pressure; **CoA:** coenzyme A; **DKA:** diabetic ketoacidosis; **FFA:** free fatty acid; **GLUT:** glucose transporter; **HDL:** high-density lipoprotein; **HF:** heart failure; **IL:** interleukin; **MCD:** malonyl CoA decarboxylase; **MR:** magnetic resonance; **NFκB:** nuclear factor kappa B; **PPAR:** peroxisome proliferator-activated receptor; **TMZ:** trimetazidine; **T2DM:** type 2 diabetes mellitus; **UCP:** uncoupling protein

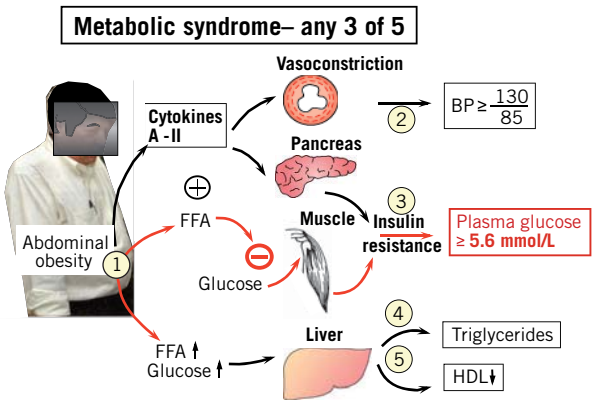

Fig. 1 *The metabolic syndrome potentially consists of five clinical components, namely abdominal obesity, high blood TGs, low HDL-cholesterol levels, prehypertension (BP equal to or above 130/85 mm Hg) or higher, and hyperglycemia. A proposed sequence of events that could lead to this syndrome is as follows. Excess calories and too little exercise give rise to abdominal adiposity. From there, increased FFAs are released into the circulation, thereby inhibiting the uptake of glucose by muscle. Plasma glucose rises and elicits an insulin response. Adipose tissue also releases cytokines such as tumor necrosis factor alpha, which alter the insulin receptor substrate 1 so that insulin signaling is deficient. Increased release of angiotensin II from the abdominal fat causes vasoconstriction and increases the BP. The net overall effect is insulin resistance with increased fasting plasma glucose despite the increased circulating insulin. Increased plasma FFAs and glucose predispose to increased hepatic synthesis of TGs and increased blood levels of TGs, which in turn decrease levels of HDL-cholesterol. Note that an increased total cholesterol level is not part of the syndrome. BP, blood pressure; CoA, coenzyme A; FFA, free fatty acid; HDL, high-density lipoprotein; TG, triglyceride*

significance, but when taken together indicate an enhanced risk of developing overt diabetes or cardiovascular disease. The risk of developing future cardiovascular problems is proportional to the number of features of the metabolic syndrome [7]. The basic metabolic abnormality in the metabolic syndrome is excess abdominal adipose tissue, which is a metabolically active organ [7] and liberates excess circulating FFAs [6]. The inhibitory effect of plasma FFAs on insulin signaling follows a rather modest increase in plasma FFAs, developing at concentrations that are well within the physiological range at plasma FFA levels observed in obesity and T2DM [8], and hence found in the metabolic syndrome.

Molecular steps leading from increases in blood FFAs to insulin resistance

Excess FFAs entering the muscle cell is activated to long-chain acyl coenzyme A (CoA), which inhibits the insulin signaling pathway so that there is less translocation of glucose transporter vesicles (GLUT-4 and GLUT-1) to the cell surface to increase glucose uptake. Glucose uptake is decreased and hyperglycemia promoted. The increased uptake of FFAs promotes lipid metabolite accumulation in various organs including the heart and pancreas. Exercise and the antidiabetic drug metformin, by stimulating the enzyme AMP-activated protein kinase (AMPK), both promote the translocation of glucose transport vesicles to the cell surface to promote glucose entry and to oppose insulin resistance [9].

Role of hyperglycemia

The choice of diet could help to control hyperglycemia. The higher intake of vegetables, fruits, nuts, whole grains, and a lower intake of red meat could reduce the risk of T2DM as shown in a review of 48 studies [10]. Furthermore, in T2DM adherence to the Mediterranean diet can help to control hyperglycemia [11]. Olive oil in liberal amounts is a crucial component of the Mediterranean diet, because in T2DM it delays gastric emptying and attenuates the postprandial increases in glucose, insulin, and the glucose-dependent insulinotropic polypeptide, while increasing glucagon-like peptide 1 [12].

Cardiovascular risks of metabolic syndrome

First, it should be emphasized that the metabolic syndrome comprises a group of cardiovascular risk factors, namely abdominal obesity, high blood triglycerides, low HDL-cholesterol levels, high normal BP hypertension and hyperglycemia, which when taken together indicate enhanced risks of the development of overt diabetes or cardiovascular disease. There is doubt as to whether every one of the five components of the metabolic syndrome could singly predict the development of diabetes [13]. Others have emphasized the predictive value of two components

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of the metabolic syndrome, modest elevations of glucose and BP, which were mostly responsible for increasing the cardiovascular risk by 71% [14]. For cardiologists, becoming alert to the clustering of these risk factors is an important widening of clinical vision [15]. The risk of the metabolic syndrome developing into future cardiovascular events is proportional to the number of metabolic syndrome features [16]. With four or five features, the risk of diabetes was 25-fold greater than with no features and still much more than with only one feature [17]. In an important definitive analysis of 172 573 persons in 37 studies, the metabolic syndrome had a relative risk of 1.78 for future cardiovascular events, significant even after adjusting for more traditional cardiovascular risk factors (relative risk 1.54) [18].

Insulin resistance

Insulin resistance leads to the metabolic syndrome [19] and increased circulating FFAs and glycemia, plus elevated glucose production in the liver, which are precursors of T2DM [20]. There is a dose–response effect of elevated plasma FFAs on insulin signaling [21]. Experimentally, cardiac insulin resistance with decreased production of ATP is found in pressure overload hypertrophy, preceding the development of systolic HF [22].

Where does obesity enter the picture? Obese persons have high blood FFA levels, which even at modest elevations inhibit insulin signaling and stimulate nuclear factor kappa B (NFκB) to promote insulin resistance (see Figure 1 in Kim) [23]. NFκB in turn stimulates macrophages to provoke the chronic low-grade inflammatory response (see Figure 2 in Kim) [23] with increased plasma levels of C-reactive protein, and inflammatory cytokines such as tumor necrosis factor alpha, interleukin (IL)-6, monocyte chemoattractant protein 1 and IL-8. Macrophages in human adipose tissue are the main but not the only source of these inflammatory mediators that stimulate insulin resistance in multiple organs [23]. The "western" type high-fat diet experimentally enhances such cytokine production, whereas exercise diminishes it [24].

Obesity: → high FFAs → molecular signaling (NFκB, others) → macrophages → inflammatory cytokines → insulin resistance → risk of diabetes

Molecular steps in diabetes leading from increased FFAs to insulin resistance

Excess FFAs entering the muscle cell are activated to long-chain acyl CoA, which inhibits the insulin signaling pathway so that there is less translocation of glucose transporter vesicles (GLUT-4 and GLUT-1) to the cell surface (see *Figure 1*). Glucose uptake is decreased and hyperglycemia promoted. The increased uptake of FFAs promotes lipid metabolite accumulation in various organs including the heart and pancreas. Metformin and exercise, by stimulating AMPK, promote the translocation of transport vesicles to the cell surface to promote glucose entry and to oppose insulin resistance. Protein kinase B, also called Akt, plays a key role. These changes are reviewed elsewhere [25]. When compared with glucose as myocardial fuels, excess FFAs as in the metabolic syndrome are ATP-wasting (see next section).

Changes in fatty acid and glucose metabolism that occur in diabetes

In a genetic animal model of T2DM, the db/db mouse, there was a major decrease in the cardiac efficiency of work, with an 86% increase in unloaded myocardial oxygen consumption [26]. Furthermore, the angle of the pressure–volume area/oxygen consumption measured during work had a steeper slope, suggesting reduced efficiency of cardiac work. This implies a negative inotropic effect (see Figure 3.8 in Opie) [27] and decreased efficiency of work. These changes reflect the adverse effects of the high blood FFAs, about double normal [26], which imply decreased glucose utilization and increased fatty acid oxidation. Acute elevation of the FFA supply in both normal and db/db mouse hearts increased myocardial oxygen consumption due to the increased oxygen cost for basal metabolism and for excitation–contraction coupling. Beta-adrenergic stimulation, on top of a high fatty acid supply, led to a further increase in the unloaded myocardial oxygen consumption [28]. There is thus a firm link in this model between FFA levels and adverse effects on the heart.

Likewise, In patients with T2DM the increased plasma FFA levels have adverse effects on ATP, as will be discussed in the next section [29]. The onset of diabetes and its progression can be delayed by lifestyle interventions including weight loss and exer-

cise [30]. In particular, robust weight loss in response to bariatric surgery not only ameliorates circulating glucose, insulin, and FFA levels, but also normalizes cardiac diastolic function [31].

Possible metabolic therapies

There are a number of interventions including glucose–insulin–potassium [32] and trimetazidine (TMZ) that can reduce the abnormalities of excess FFA metabolic breakdown (*Figure 2*). TMZ is a metabolically

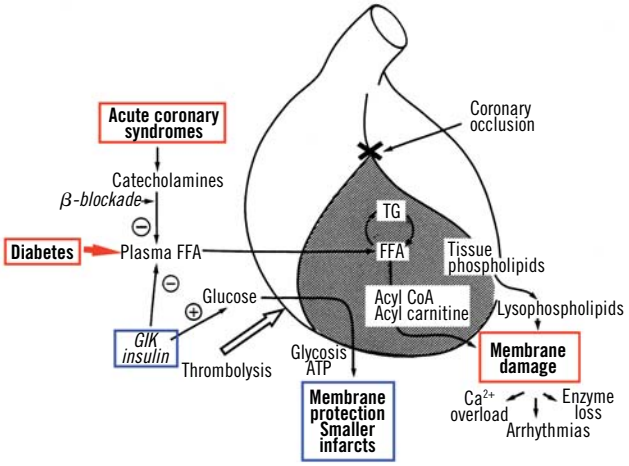

Fig. 2 *In diabetes, increased levels of circulating FFAs indirectly lead to metabolic inefficiency (see text) and membrane damage, whereas the promotion of glycolysis by providing glycolytic ATP and increasing metabolic efficiency gives membrane protection. Note that in acute coronary syndromes similar principles of metabolic cardioprotection apply [32]. Circulating FFAs may be reduced both by β-blockade and by infusion of glucose–insulin–potassium with therapeutic benefit. BP, blood pressure; CoA, coenzyme A; FFA, free fatty acid; GIK, glucose-insulin-potassium; HDL, high-density lipoprotein; TG, triglyceride*

active antianginal agent widely used in Europe but not licensed in the USA. TMZ has multiple potentially cardioprotective mechanisms besides partial inhibition of FFA oxidation, together with increased glucose oxidation as found in isolated rat hearts [33, 34]. In patients with T2DM and HF, TMZ induced an increase in peripheral muscle glucose oxidation and decreased fatty acid oxidation (as measured by citrate release) [35].

ATP wastage with FFA use in diabetic states

Experimental data

ATP wastage implies uncoupling of oxygen consumption by the respiratory chain from ATP synthesis. Mitochondria are regarded as the major source of reactive oxygen species [36]. Excess circulating FFAs, as in uncontrolled diabetes, may inhibit ATP transfer from mitochondria to cytosol [37]. Furthermore, excess uptake of FFAs by cardiac myocytes leads to an increase in long chain acyl CoAs in the mitochondrial matrix [37]. Uncoupling proteins (UCPs) are anion carriers expressed in the mitochondrial inner membrane that uncouple oxygen consumption by the respiratory chain from ATP synthesis. Their net effect is proton leakage [37]. At any given level of cardiac work, primary use of FFA rather than glucose can decrease the efficiency of work by 10–25% [37] and oxygen wastage by over 40% [38]. FFAs also inhibit pyruvate oxidation, thereby further promoting the switch away from glucose metabolism. Overall, predominant and excessive use of FFAs as myocardial fuel can cause ATP wastage by multiple mechanisms.

ATP wastage may also be generated by UCPs. Mitochondria from genetically diabetic db/db mice have fatty acid-induced mitochondrial uncoupling that may be mediated by UCPs with the isoform subtype not specified [39]. Furthermore, and controversially, UCPs may play a role in the pathogenesis of diabetes mellitus, as recently reviewed [40]. UCP-1 is considered to be a candidate gene for diabetes because of its role in thermogenesis and energy expenditure. UCP-2 is expressed in several tissues and acts in the negative regulation of insulin secretion by β cells and in fatty acid metabolism. UCP-3 plays a role in fatty acid metabolism and energy homeostasis and modulates insulin sensitivity. Of these, UCP-3 is proposed as playing an essential role in the mitochondrial adaptation to fasting in that mitochondria of ucp3$^{-/-}$ mice exhibited impaired fatty acid oxidation with consequential matrix accumulation of palmitate [41].

In the diabetic state, potentially cardioprotective glucose metabolism is regulated not only by FFA–glucose interaction, but also by malonyl decarboxylase (MCD). This key enzyme is highly regulated by peroxisome proliferator-activated receptor (PPAR)-α and its activity and expression is increased in diabetes [37]. Conversely, selective MCD inhibitors increase myocardial malonyl CoA content and stimulate glucose metabolism, which is turn will reduce FFA-induced ATP wasting [37].

Lipotoxicity and diabetic cardiomyopathy

High circulating fatty acids predispose to lipotoxicity and contribute to insulin resistance. Cytoplasmic ac-

cumulation of lipid metabolites results in contractile dysfunction and thus may contribute to the cardiomyopathies found in obesity and diabetes [37]. How does this apply to myocardial ATP wastage? The underlying etiology of diabetic cardiomyopathy can be related to cardiac lipotoxicity [42] thus indirectly contributing to myocardial ATP wastage. Furthermore, in patients with diabetes and/or obese patients with severe end-stage idiopathic dilated cardiomyopathy and a mean ejection fraction of19%, referred for cardiac transplantation, intramyocardial lipid overload was found in about one-third of the hearts, especially in patients with diabetes and obesity (body mass index >30) [43].

Skeletal muscle also suffers [44]. In patients with T2DM proton nuclear magnetic resonance (MR) could detect intramyocellular fat as long chain fatty acyl CoA in biopsies. Treatment of such patients to reduce insulin resistance by the PPAR-γ agonist, pioglitazone, reduced both intramyocellular triglyceride content and skeletal muscle long chain fatty acyl CoA. The latter decrease strongly correlated with enhanced insulin sensitivity. The term lipotoxicity thus has widespread implications with links to many metabolic abnormalities in T2DM, metabolic syndrome and advanced HF.

Myocardial lipid abnormalities in patients with aortic stenosis

Myocardial steatosis, the condition of abnormal lipoid deposits in myocardial cells, has been associated with obesity, impaired glucose tolerance, and T2DM. Those studies showed that myocardial triglyceride content was an independent correlate of both systolic and diastolic dysfunction, implying a causal relationship between steatosis and such functional changes [45]. In this novel observation, 39 patients with severe aortic stenosis but with normal left ventricular ejection fraction and similar blood levels of FFAs, glucose, triglycerides, and lipoproteins, but without significant coronary artery disease and 20 matched healthy controls were studied. They underwent cardiac 1H-MR spectroscopy and imaging for the determination of steatosis (myocardial triglyceride content). Left ventricular function tests included circumferential strain (measured by MR tagging). Strain was decreased in both symptomatic and asymptomatic patients but more so in those with symptoms (–16.4 ± 2.5% and –18.1 ± 2.9%, respectively, versus controls –20.7 ± 2.0%, both $P < 0.05$). Myocardial steatosis was found in both symptomatic and asymptomatic patients (0.89 ± 0.42% in symptomatic; 0.75 ± 0.36% in asymptomatic versus controls 0.45 ± 0.17, both $P < 0.05$). Importantly, multivariable analysis indicated that steatosis was independently correlated to impaired left ventricular strain. Pronounced myocardial steatosis was thus present in severe aortic stenosis, regardless of symptoms, and was independently associated with the degree of left ventricular strain impairment.

Lipotoxicity has been implicated in the development of muscle insulin resistance and T2DM [44], which implies that this lipid abnormality can further be linked to defective ATP metabolism as an early abnormality in these apparently asymptomatic patients. The further hypothesis would be that abnormal myocardial mechanical strain from other chronic valve abnormalities could also suffer from superadded lipid abnormalities that could potentially contribute to increasingly abnormal left ventricular function.

Hypothesis: Mechanical defect → increased left ventricular strain → unknown signaling → lipoid deposits in left ventricle → metabolic ATP wastage

ATP wastage in patients with T2DM

Although a specific biochemical-based diabetic cardiomyopathy has long been suspected [46], with experimental proof in 1997 [47], the clinical problem in defining a pure diabetic metabolic heart disease has been frequent concurrent diabetic coronary artery disease [48]. Focusing on the diabetic myocardium, Taegtmeyer et al [48] introduced the concept of glucolipotoxicity, reflecting the adverse myocardial effects of excess circulating FFAs and the consequent block in cardiac metabolism at the level of inhibited glucose uptake and glycolysis at the level of pyruvate dehydrogenase, with insulin giving rise to high circulating glucose levels. In combination, these are the metabolic changes that lead to myocardial ATP wastage.

To prove that ATP wastage occurs in human diabetic cardiomyopathy, Scheuemann-Freestone et al [29] studied patients with diabetes but without coronary heart disease or evidence of clinical HF. They found a complex metabolic disequilibrium associated with insulin resistance and accompanied by

decreased cardiac phosphocreatine to ATP ratios. Furthermore, there was impaired post exercise recovery of skeletal high-energy phosphate. Cardiac high-energy phosphate metabolites were measured at rest using 31P nuclear MR spectroscopy. Although their cardiac morphology, mass, and function appeared to be normal, the patients with diabetes had lower phosphocreatine/ATP ratios than the healthy volunteers. Of interest is the fact that the cardiac phosphocreatine/ATP ratios correlated negatively with the fasting plasma FFA concentrations. Furthermore, there was impaired post exercise recovery of skeletal high-energy phosphate compounds. Proof of metabolic ATP wastage was decreased cardiac levels of phosphocreatine and ATP.

Proposal: Metabolic defect in T2DM → increased FFA and less glucose usage → less ATP synthesis → metabolic ATP wastage

Diabetic coma

There is no exact replica of this complex human condition, yet relevant to the human condition of type 1 diabetes with coma is the study by How et al [49] on genetically diabetic db/+ mice given streptozotocin in a model with reduced body and heart weights, without elevations in plasma FFA levels. Plasma glucose concentrations were very high (mean 31.8 mmol/L) with ketosis. Stage 3 respiration decreased in mitochondria incubated with either palmitoyl-carnitine or pyruvate. Diabetic hearts showed decreased cardiac efficiency, with an 86% increase in unloaded myocardial oxygen uptake. The corresponding human condition seen in type 1 diabetes is pure diabetic ketoacidosis (DKA) without significant hyperosmolarity, which typically indicates the total or relative absence of insulin [50].

Although the pathogenesis of the hyperosmolar hyperglycemic diabetic comatose state is less well understood than that of DKA, the basic underlying mechanism for both disorders is a reduction in the net effective action of circulating insulin, ie, insulin resistance [50]. This state, but without ketoacidosis, typically occurs with lesser degrees of insulin deficiency, as seen in T2DM. However, there is usually a mixed clinical presentation depending on the duration of symptoms, coexisting medical illnesses, or underlying precipitating cause. Diabetic coma is thus a complex and varying metabolic illness that results from a combination of major insulin resistance and increased activity of the counterregulatory hormones, including catecholamines.

Conclusion

The adverse myocardial metabolic effects of hyperglycemia, the metabolic syndrome, and the diabetic state are analyzed with special reference to: the metabolic syndrome, obesity, and insulin resistance as precursors to T2DM; the inhibitory effects on glucose metabolism of high blood FFA levels leading to insulin resistance; the changes in fatty acid and glucose metabolism that occur in diabetes; and the significance of these changes of wastage of energy in the form of ATP depletion. ■

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