Diabetic Gluco-lipotoxic Cardiomyopathy – Amendable by Metabolic Manipulation?

a report by
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Type 2 diabetes has grown to epidemic proportions and it is estimated that 4.4% of the global population will be affected by 2030.¹ Patients with type 2 diabetes are at an increased risk of cardiovascular disease, in particular coronary artery disease (CAD) and heart failure; consequently, heart disease is the most common cause of death in type 2 diabetes.² In asymptomatic patients, cardiac structural and functional abnormalities exist even in the absence of CAD or hypertension due to diabetic cardiomyopathy (DCM).³ Left ventricular (LV) diastolic dysfunction is a common and early finding that, particularly in the presence of cardiac ischaemia, may develop into overt heart failure.⁶ Although DCM is a multifactorial condition, diabetes-related metabolic derangements seem to be key contributors to the observed cardiac abnormalities.⁵ This article focuses on the potential role of myocardial metabolic changes in cardiac dysfunction in human diabetes. Furthermore, current therapeutic options that may affect cardiac metabolism and their clinical consequences are summarised.

Background and Epidemiology

Large population-based studies in people with diabetes using echocardiography⁴ and, more recently, cardiac magnetic resonance (CMR)⁸ have identified myocardial structural and functional abnormalities, including increased LV mass and relative wall thickness, a reduced endocardial and mid-wall fractional shortening and, most importantly, an increased prevalence of LV diastolic dysfunction, collectively providing evidence for the existence of DCM.⁸ In fact, LV diastolic filling abnormalities can already be found in obese and insulin-resistant individuals and in those with the metabolic syndrome.⁴,¹¹,¹² Before structural abnormalities become manifest in type 2 diabetes, 60% of patients without CAD or diabetes-related complications already show LV filling abnormalities.¹³ The progressive nature of LV dysfunction in diabetes is illustrated by the two- to eight-fold increase in congestive heart failure (CHF) in this population, with risk ratios twice as large in women compared with men.¹⁴,¹⁵ Conversely, approximately 19% of CHF patients have diabetes, and CHF is strongly associated with the presence of insulin resistance.¹⁶ In the Uppsala Longitudinal Study of Adult Men (ULSAM), insulin resistance predicted CHF incidence independently of diabetes and other established risk factors.¹⁷

Pathophysiology of Diabetic Cardiomyopathy

DCM was first described by Rubler et al. in 1972 as a separate disease entity based on post mortem findings in four diabetic patients with nephropathy and heart failure who appeared to have normal coronary arteries at autopsy.¹¹ These authors then suggested that the metabolic abnormalities directly related to diabetes might be implicated in the development of DCM.¹³ Since then various mechanisms have been proposed to underlie DCM in addition to the acknowledged metabolic hallmarks of the type 2 diabetes phenotype, including insulin resistance, hyperlipidaemia and hyperglycaemia, all of which are currently regarded as contributors to altered myocardial substrate handling and subsequent oxidative stress and mitochondrial dysfunction (see Figure 1). These additional mechanisms include microangiopathy, vascular endothelial function, activation of the renin–angiotensin system (RAS), inflammation, formation of glycation-induced collagen cross-links, alterations in structural and contractile proteins, interstitial fibrosis and abnormalities in calcium (Ca²⁺) homeostasis.¹⁸,¹⁹ The diabetes-related metabolic derangements are believed to negatively influence myocardial energy metabolism and ultimately contribute to the observed derangements in energy-demanding functions, including LV diastolic relaxation and contractile function.¹⁵ The formation of advanced glycation end-products (AGEs), fibrosis and microangiopathy will further aggravate myocardial stiffness, resulting in decreased LV compliance and LV filling abnormalities. Disturbances in myocardial Ca²⁺ homeostasis, most likely occurring secondary to the metabolic changes and oxidative stress,²⁰ have been associated with the LV functional abnormalities in DCM.²¹ Finally, cardiac autonomic neuropathy was shown to further aggravate LV structural and functional changes.¹⁹ Due to the versatile beneficial actions of insulin on the myocardium, impaired cardiac insulin signalling is regarded as one of the major factors underlying the development of DCM (see Figure 1).²²

Clinical Presentation and Diagnostic Procedures in Human Diabetic Cardiomyopathy

Several stages in DCM have been identified.²³,²⁴ In the early stages, patients rarely develop clinical symptoms, although early DCM was associated with a reduced exercise capacity.²⁵ Over time, especially in the presence of comorbidities such as hypertension, microangiopathy, ischaemia and cardiac autonomic dysfunction, DCM may proceed to overt CHF.²
Echocardiography is widely used in the evaluation of LV function since it is a non-invasive, readily available and inexpensive method.\textsuperscript{23,26} LV diastolic functional estimates are derived from Doppler measurements of trans-mitral inflow velocities and include the early diastolic LV filling velocity (E-wave), the atrial filling velocity (A-wave), the E:A ratio and deceleration time. The earliest stage in DCM is typified by subclinical diastolic functional changes (E:A ratio <1), with a preserved ejection fraction and normal LV wall and ventricle sizes. The next stage is characterised by further impairment of diastolic filling due to increased LV pressure and a somewhat increased LV mass and wall thickness. To meet sufficient LV filling, left atrial (LA) pressure will gradually increase over time, resulting in an echocardiographical inflow pattern that is indistinct from normal (pseudonormal) and is regarded as an intermediate phase. A further increase in LA pressure leads to a restrictive filling pattern (E/A ratio >2), leading to a reduction in ejection fraction and the development of clinical symptoms of CHF.

Conventional echocardiography may be insensitive to detect subtle functional alterations, especially to discriminate between normal and pseudonormal diastolic function, thereby potentially underestimating the prevalence of DCM.\textsuperscript{23,24} TheValsalva manoeuvre and assessment of pulmonary venous flow can be used to uncover the otherwise undetected diastolic functional abnormalities. Tissue Doppler imaging (TDI) is relatively insensitive to the effects of pre-load compensation and can overcome the limitations of conventional echocardiography.\textsuperscript{23,26} Novel methods including computed tomography (CT) and cardiovascular magnetic resonance imaging (CMR) are increasingly being employed to quantify LV systolic and diastolic function as these methods are operator-independent, and therefore highly reproducible.\textsuperscript{26} The B-type natriuretic peptide (BNP) (or NT-proBNP) level is a useful marker in the evaluation of heart failure, hypertrophy and CAD.\textsuperscript{27,28} Screening for LV dysfunction in diabetes using BNP may have potential in high-risk symptomatic patients but not in asymptomatic individuals without overt vascular disease.\textsuperscript{29-31} In a cohort of high-risk type 2 diabetes patients without structural heart disease and normal ejection fraction, BNP levels were similar in patients with and without LV diastolic dysfunction.\textsuperscript{32} Currently, TDI and CMR are regarded as the most reliable tools for the detection of subclinical LV dysfunction.

Methods for In Vivo Assessment of Myocardial Metabolism in Humans

Pioneering studies measuring arterial-coronary sinus differences in myocardial substrate concentrations to evaluate myocardial metabolism in humans stem from the middle of the last century.\textsuperscript{33,34} This technique was later expanded by the additional use of labelled substrates such as \textsuperscript{14}C-palmitate and \textsuperscript{13}C-oleic acid.\textsuperscript{35} The development of dedicated tracers for single-photon emission computed tomography (SPECT) and positron emission tomography (PET) has further increased our insight into human myocardial substrate handling in health and disease.\textsuperscript{36,37} Only PET allows the quantification of metabolic processes using tracers to assess myocardial glucose, lactate and fatty acid (FA) and oxidative metabolism (see Figure 2). The uptake and processing of tracers in the heart depend on tracer specific properties. Thus, the glucose analogue 2-deoxy-\textsuperscript{18}F]-fluoro-D-glucose (\textsuperscript{18}F-FDG) is trapped following uptake and phosphorylation to FDG-6-phosphate, thereby representing the transmembrane uptake and phosphorylation of exogenous glucose. The fatty acid analogue 14(R,S)-\textsuperscript{18}F]-fluoro-6-thia-heptadecanoic acid (\textsuperscript{18}F-FTHA) is used to estimate \(\beta\)-oxidation as it is partially oxidised with

Cardiac substrate uptake, including non-esterified fatty acids (NEFAs) glucose and lactate, is largely receptor-mediated; however, NEFAs may enter the cell by diffusion. Following uptake, NEFAs are converted to fatty acyl-CoAs that are transported into the mitochondria through carnitine palmitoyltransferase (CPT) 1 and 2. There fatty acyl-CoAs undergo \(\beta\)-oxidation (\(\beta\)-ox), generating acetyl-CoAs and the reducing equivalents nicotinamide adenine dinucleotide (NADH) and flavin adenine dinucleotide (FADH). Acyl-CoAs can also be esterified into triglycerides. Intramitochondrial glucose is degraded to pyruvate, generating adenosine triphosphate (ATP) and NADH. Anaerobic degradation of glucose can also lead to the generation of lactate. In the presence of oxygen, pyruvate is transported into the mitochondria through the multimeric complex pyruvate dehydrogenase (PDH). Pyruvate is converted to acetyl-CoA, with the formation of NADH, and fatty acyl-CoAs are converted to acetyl-CoA, with formation of NADH and FADH. Oxidation of acetyl-CoAs in the citric acid or tricarboxylic acid (TCA) cycle generates CO\(_2\) and guanosine triphosphate (GTP) as well as NADH and FADH. Electrons (e\(^-\)) derived from NADH/FADH\(_{2}\) are transferred via electron-transport complexes I to IV from the electron transport chain (ETC). Here, electrons are transferred to oxygen, which is then reduced to water and consequently a proton (\(\text{H}^+\)) gradient is formed. As protons re-enter the mitochondria through ATP-synthase, ATP is generated from adenosine-diphosphate (ADP). Cardiac substrate and oxidative metabolism in humans can be assessed non-invasively by positron emission tomography (PET) or single-photon emission computed tomography (SPECT) using dedicated tracers (displayed in rectangles below their natural substrates). Cardiac molecular imaging is used to assess several metabolic processes (displayed in oval), myocardial triglyceride content (\(13\text{C}-\text{MRS}\)), mitochondrial high-energy metabolism (\(13\text{C}-\text{MRS}\)) and pyruvate metabolism (\(13\text{C}-\text{MRS}\)). For description tracers see text.
Diabetes and Cardiovascular Risk

Although the relative distribution of \( ^{18}F \)-FDG already yields information about cardiac metabolism, the myocardial metabolic rate of glucose uptake (MMRglu) can be measured in absolute units. To measure MMRglu, both dynamic data acquisition and graphical plot or compartmental model analysis are required.\(^{42-44} \) Compartmental modelling is a mathematical approach also used in the analysis of 11C-tracers that describes the actual rate of tracer processing through several pre-defined physiological compartments and requires the determination of radioactive metabolites such as \( ^{11}C \)O\(_2\) and/or \( ^{11}C \)lactate for additional correction in order to obtain reliable kinetic results.\(^{45-47} \) Exponential curve fitting is an alternative, though less accurate, method that yields a useful index of tracer oxidation.\(^{48} \)

The more recent development of cardiovascular molecular imaging enables the imaging and quantification of molecular and cellular targets in humans in vivo. Current MR spectroscopy (MRS) techniques such as phosphorus magnetic resonance spectroscopy (\( ^{31}P \)-MRS) and proton magnetic resonance spectroscopy (\( ^{1}H \)-MRS) are used for the respective assessment of myocardial high-energy phosphate metabolism expressed as the phosphocreatine:adenosine triphosphate (PCr:ATP) ratio, thus representing myocardial mitochondrial function\(^{49} \) and myocardial lipid content\(^{50} \). Novel developments include molecular imaging with \( ^{19}F \) and \( ^{13}C \).\(^{51} \) The high potential of this metabolic imaging technique was previously shown in rats and pigs using polarised \( ^{13}C_1 \)-pyruvate nuclear MRS, which allowed quantification of the distribution of pyruvate and mapping of its major metabolites, lactate and alanine.\(^{52} \) Moreover, multiparametric MRI by the combined use of \( ^{1}H \), \( ^{19}F \) and \( ^{13}C \) will have great potential to monitor and quantify biological processes and localise them in space and time.\(^{51} \)

**Substrate Metabolism and the Role of Insulin Signalling in the Normal Heart**

Under physiological conditions, the normal heart primarily utilises non-esterified fatty acids (NEFA), but also glucose and, to a lesser extent, lactate, ketones, amino acids and pyruvate in order to produce sufficient ATP to sustain contractile function (see Figure 2).\(^{11,14} \) The major part of ATP is produced by mitochondrial oxidative metabolism, which consumes large amounts of oxygen. In the well-oxygenated heart, FA \( \beta \)-oxidation provides approximately 60–90% of the required ATP, whereas carbohydrate metabolism provides most of the remaining 10–40%.\(^{15} \) Of note, when NEFA are the substrate, oxidation of one mole of carbon yields 29% more ATP compared with glucose; however, one mole of oxygen produces 12% more ATP when glucose is the substrate compared with NEFA.\(^{56} \) During daily physiological activities, but even more so under stress conditions such as ischaemia, the heart can readily switch to the most advantageous substrate according to the circumstances, and as such may be regarded as a metabolic omnivore.\(^{11,14} \) NEFA utilised by the heart may be either circulating NEFA, bound to albumin, derived from adipose tissue via lipolysis or released from triglyceride-rich lipoproteins by hydrolysis via lipoprotein lipase.\(^{57} \) NEFA are taken up by cardiomyocytes by diffusion and via transport through plasma-membrane-associated proteins, including the main transporter, FA translocase (FAT/CD36, as well as FA binding protein (FABP) and FA transport proteins (FATP1 and FATP6).\(^{58-60} \) Cytosolic NEFA bind to FABP and are subsequently transported to acyl-CoA by fatty acyl-CoA synthase. The main part of acyl-CoA is transported into mitochondria via a carnitine-dependent transport system, to undergo \( \beta \)-oxidation to acetyl-CoA, which then enters the TCA cycle (see Figure 2). A small portion is converted to triglycerides or phospholipids.\(^{60} \) Carnitine palmitoyl transferase (CPT)-1, the key enzyme involved in FA oxidation that is located on the outer mitochondrial membrane, is inhibited by malonyl-CoA, which in turn is regulated by AMP-activated protein kinase (AMPK).\(^{61} \)

Glucose is supplied to the heart either via the circulation or by release of glucose from intracellular glycogen stores.\(^{62} \) Exogenous glucose is taken up via facilitated transport in proportion to ambient glucose levels through the glucose transporter GLUT1, which is insulin-independent, and the predominant GLUT4, which is regulated by insulin.\(^{63} \)

Intracellular glucose is phosphorylated to glucose-6-phosphate by a hexokinase, and may subsequently be converted to glycogen and enter the glycolysis pathway or the pentose phosphate pathway. Under aerobic conditions, glycolysis, which is controlled by the rate-limiting enzyme phosphofructokinase (PFK)-1,\(^{64} \) accounts for approximately 10% of ATP formation, ultimately yielding two molecules of pyruvate and two NADH per molecule of glucose. Pyruvate and NADH are shuttled into the mitochondria, where the pyruvate dehydrogenase (PDH) complex synthesises acetyl-CoA from the pyruvate; this acetyl-CoA then enters the TCA cycle.\(^{65} \) Regulation of glucose metabolism occurs at the level of uptake, as AMPK stimulates translocation of cytosolic GLUT4 to the sarcolemma, as well as at the level of metabolism, where the rate-limiting enzyme of the glycolytic pathway PFK-1 can be inhibited by ATP, low pH and fructose-1,6-phosphate and activated by ADP, AMP and free phosphate. Additional regulation occurs at the level of PDH that can become inactivated by pyruvate dehydrogenase kinase (PDK), or inhibited by acetoacetyl-CoA, NADH and ATP.

Insulin regulates myocardial substrate uptake and metabolism both indirectly, by acting on its target organs and therefore regulating substrate availability, and by directly acting on the myocardium. Thus, impaired insulin signalling will lead to elevated circulating NEFA and glucose levels due to unsuppressed lipolysis from adipocytes, increased hepatic output of very-low density lipoprotein (VLDL)-triglycerides and elevated hepatic glucose production.\(^{22} \) At the level of the heart, insulin regulates NEFA and glucose uptake by stimulating the translocation of GLUT4 and CD36 to the sarcolemma.\(^{14} \) Following insulin stimulation, glucose is mainly oxidised or stored as glycogen, while NEFA are diverted towards esterification into triglycerides.\(^{66} \) Finally, adipokines such as leptin and adiponectin exert significant metabolic actions on the heart\(^{72} \) by the activation of AMPK; however, currently their role in human DCM is unknown.

**Myocardial Lipotoxicity and Insulin Resistance**

In animal models of insulin resistance and diabetes, myocardial insulin resistance is associated with reduced cardiac glucose and increased FA metabolism.\(^{72,84} \) In a rat model of diet-induced insulin resistance, decreased glucose uptake was associated with impaired insulin signalling and enhanced rates of NEFA uptake were associated with the sustained sarcolemmal presence of CD36.\(^{60} \) When NEFA uptake surpasses mitochondrial oxidative capacity, formation of toxic intermediates ensues, as well as generation of reactive oxygen species (ROS), mitochondrial dysfunction and activation of pro-apoptotic pathways paralleled by increased esterification of NEFA into triglycerides. Increased NEFA utilisation is additionally associated with mitochondrial uncoupling, which leads to decreased ATP production and consequently to reduced cardiac efficiency.\(^{73} \) NEFA also serve as natural ligands for peroxisome
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In human obesity-related insulin resistance and diabetes, several invasive and non-invasive approaches (outlined above) have been used in the search for evidence of the existence of cardiac lipotoxicity. Although the number of human studies is limited, increased myocardial lipid content was found in myocardial biopsy samples from obese individuals and patients with CHF using oil-red O staining. In addition, using 1H-MRS, increased myocardial lipid content was reported in obesity and patients with CHF without hypertension. However, evaluation of myocardial FA metabolism with FA tracers using SPECT and PET in various populations with different glucometabolic characteristics, including the presence of co-morbidities, the use of medications and the severity and duration of metabolic deregulation, but also methodological issues such as the use of different insulin medications and the severity and duration of metabolic deregulation, but also methodological issues such as the use of different insulin concentrations when assessing insulin-stimulated glucose uptake. Finally, the inclusion of both sexes in these studies may also have influenced results, since glucose extraction fraction and utilisation but not fatty acid oxidation, thus leaving the question regarding the occurrence of myocardial lipotoxicity in humans unresolved (see Table 1).

For a long time the existence of myocardial insulin resistance has been debated, since traditionally the heart was neglected as a target organ for insulin signalling. Using PET technology, several studies have assessed insulin signalling. Using PET technology, several studies have assessed the occurrence of myocardial lipotoxicity in various (pre-)diabetic populations; however, these studies have yielded conflicting results (see Table 1) due to differences in subject characteristics, including the presence of co-morbidities, the use of medications and the severity and duration of metabolic deregulation, but also methodological issues such as the use of different insulin concentrations when assessing insulin-stimulated glucose uptake. Finally, the inclusion of both sexes in these studies may also have influenced results, since glucose extraction fraction and utilisation but not fatty acid oxidation, as well as unaltered, increased or decreased FA uptake, as well as unaltered, increased or decreased FA uptake, as well as unaltered, increased or decreased FA uptake, as well as unaltered, increased or decreased FA uptake, as well as unaltered, increased or decreased FA uptake, as well as unaltered, increased or decreased FA uptake, as well as unaltered, increased or decreased FA uptake, as well as unaltered, increased or decreased FA uptake, as well as unaltered, increased or decreased FA uptake, as well as unaltered, increased or decreased FA uptake.
metabolism are lower in women. By performing \(^{18}\)F-FDG PET under standardised hyperinsulinaemic-euglycaemic clamp conditions in well-characterised patient groups, i lozzo et al. have convincingly shown that insulin-stimulated \(^{18}\)FDG uptake was reduced in patients with type 2 diabetes with, as well as in those without, CAD, but not in type one diabetes patients (see Table 1).

**Glucose Toxicity and Oxidative Stress**

The mechanism whereby chronic hyperglycaemia mediates tissue injury through the generation of ROS has been elucidated largely through the work of Michael Brownlee and colleagues. Hyperglycaemia leads to increased glucose oxidation and mitochondrial generation of superoxide. In turn, excess superoxide leads to DNA damage and activation of poly (ADP ribose) polymerase (PARP) as a reparative enzyme. However, PARP also mediates the ribosylation and inhibition of glyceraldehyde phosphate dehydrogenase (GAPDH), diverting glucose from its glycolytic pathway and into alternative biochemical pathways that are regarded as mediators of hyperglycaemia-induced cellular injury. Among these are increases in AGEs, increased hexosamine and polyol flux and activation of classical isoforms of protein kinase C. In addition to hyperglycaemia-associated ROS formation, the elevated NEFA flux through the \( \beta \)-oxidation cascade will also result in an increased supply of reducing equivalents to the mitochondrial electron transport chain, which will ultimately lead to increased ROS production.

It may not be easy to obtain direct evidence for these mechanisms to occur in human DCM. However, high glycated haemoglobin (HbA\(_1c\)) indicating longstanding hyperglycaemia was found to be related to impaired LV diastolic as well as systolic function in type 1 diabetes and type 2 diabetes patients. Furthermore, increased serum AGE levels were associated with LV stiffness in type 1 diabetes patients, whereas in type 2 diabetes patients serum AGE levels were increased and even higher when CAD was present. Finally, in ischaemic CHF patients, cardiac biopsy analysis showed increased myocardial AGEs deposition in diabetic CHF patients.

Increased myocardial oxygen consumption and decreased cardiac efficiency in obesity and diabetes may contribute to the development of cardiac dysfunction by increased mitochondrial uncoupling.

**Mitochondrial Dysfunction**

Mitochondrial dysfunction plays a role in DCM according to various lines of evidence. Accordingly, structural and functional mitochondrial changes have been demonstrated in several rodent models of diabetes. A reduction in mitochondrial oxidative capacity has been documented in animal models of type 1 diabetes. Decreased protein expression of the oxidative phosphorylation components, i.e. creatine phosphate activity, ATP synthase activity and creatine-stimulated respiration, were previously described. Moreover, increased myocardial oxygen consumption and decreased cardiac efficiency in obesity and diabetes may contribute to the development of cardiac dysfunction by increased mitochondrial uncoupling. Recent studies in humans have provided support for a role of mitochondrial dysfunction in DCM. In permeabilised human atrial muscle fibres from diabetic and non-diabetic males undergoing routine cardiac surgery, total oxidative phosphorylation and respiratory capacity were decreased and, paradoxically, hydrogen peroxide (H\(_2\)O\(_2\)) generation in diabetic patients was increased when fibres were exposed to both carbohydrate- and NEFA-based substrates in vitro. A reduction in the PCr/ATP ratio was described in patients with type 1 diabetes and type 2 diabetes who had no evidence of CAD and was found to be associated with LV diastolic dysfunction (see Table 1). In addition, in young obese women an increase in PET-measured cardiac NEFA metabolism and a decrease in efficiency was reported (see Table 1). Taken together, these results implicate a substantial role for mitochondrial dysfunction in the development of DCM. Further studies are needed to provide data on myocardial oxygen consumption and myocardial efficiency in patients with diabetes.

**Calcium Metabolism**

Intracellular Ca\(^{2+}\) metabolism in cardiac myocytes is impaired in experimental DCM. These abnormalities include reduced activity of ATPases, including the sarcoplasmic/endoplasmic reticulum Ca\(^{2+}\)-ATPase2a (SERCA2a), decreased ability of the sarcoplasmic reticulum to take up Ca\(^{2+}\) and reduced activities of other exchangers such as Na\(^+\) Ca\(^{2+}\) and the sarcoslemmal Ca\(^{2+}\)-ATPase. Currently, there are few studies reporting the role of disturbed Ca\(^{2+}\) metabolism in human DCM. Biopsy studies in CHF patients have reported evidence for deregulated Ca\(^{2+}\) handling. In non-ischaemic CHF patients with or without diabetes versus controls, gene expression of SERCA2a was significantly depressed in patients with diabetes compared with non-diabetic controls. In patients undergoing coronary artery bypass surgery, cardiac myofilament responsiveness to Ca\(^{2+}\) was decreased by 29% in type 2 diabetes compared with non-diabetic patients, and a near significant reduction in maximum Ca\(^{2+}\)-saturated force generation was found. Thus, more studies are needed to establish the role of disturbed myocardial Ca\(^{2+}\) metabolism in human DCM.

**Linking Abnormal Metabolism to Myocardial Dysfunction**

Animal studies of DCM show concurrent impairments of cardiac metabolism and function; however, a causal relationship remains difficult to establish. The supraphysiological, relatively short-lived conditions, even in non-genetically manipulated models such as severe hyperglycaemia, exposure to extremely deficient diets and methodological limitations of cardiac metabolic and functional measurements in rodent models may not represent the human situation in which relatively mild but chronic abnormalities are at play. Although in humans there are data showing the association between systemic metabolic abnormalities and cardiac function, direct evidence supporting the existence of myocardial dysmetabolic changes as contributing to myocardial dysfunction are relatively scarce and inconsistent (see Table 1). An inter-relationship between metabolism and myocardial function in humans is suggested by the reported reversible association between changes in glycaemia and myocardial diastolic function in some but not all studies.

A large number of studies measured myocardial substrate metabolism in human DCM using SPECT and PET, but only a few concomitantly assessed cardiac function (see Table 1). Lozzo et al. reported a weak...
In the UK Prospective Diabetes Study (UKPDS) only the use of the biguanide metformin was associated with a 36% reduction in cardiovascular disease outcomes, particularly all-cause mortality.128 Accordingly, metformin, in addition to lifestyle recommendations, is currently regarded as first-line therapy in patients with type 2 diabetes according to the combined statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD).129 Although metformin has been reported to activate AMPK using 18F-FDG-PET, Hallsten et al. found no effect of metformin on insulin-stimulated myocardial 18F-FDG uptake.130 Moreover, we found metformin to decrease insulin-stimulated myocardial 18F-FDG uptake significantly.140 In addition, experimental data indicate that metformin inhibits mitochondrial complex I activity, leading to the impairment of mitochondrial function.133–134 Thus, although metformin was shown to be beneficial in the UKPDS, the reported effects on myocardial glucose uptake and mitochondrial function are not unequivocal, and therefore warrant further research. Chronic treatment with sulfonylurea increases myocardial glucose uptake independent of glycemic control in type 2 diabetes patients.135 In insulin may have direct inotropic effects,136 but may also indirectly increase LV ejection fraction by stimulating myocardial glucose uptake. Acute administration of insulin to healthy controls and to a lesser extent in type 2 diabetes patients increased LV ejection fraction.137 Whole-body insulin sensitivity was positively associated with the LV ejection fraction.138

Rosiglitazone increased myocardial glucose uptake in type 2 diabetes patients with and without CAD.130,132 Pioglitazone improved LV diastolic function with a concomitant increase in insulin-mediated myocardial glucose uptake in men with uncomplicated type 2 diabetes and no CAD, but interestingly these two phenomena were unrelated.146 Moreover, pioglitazone did not alter myocardial

correlation between insulin-stimulated myocardial 18F-FDG uptake and the ejection fraction in a pooled analysis of control, CAD and type 2 diabetes patients.83 Furthermore, an inverse association between the PCK1-ATP ratio and diastolic functional parameters was reported in pooled data from type 2 diabetes patients and controls.84 McGavock et al. found an increase in myocardial triglyceride content in obese patients with IGT and type 2 diabetes relative to lean controls, but no relationship was established with diastolic or systolic function.127 Szczepaniak et al. reported an elevated myocardial triglyceride content that was accompanied by increased LV mass and a subtle reduction of septal wall thickening, a measure of regional systolic function, in clinically healthy subjects with a wide range of body mass indices (BMIs).75 However, in that study, LV ejection fraction was unrelated to myocardial triglyceride content. We found an independent association between decreased LV diastolic functional parameters and myocardial triglyceride content as measured by MRI and 1H-MRS in well-controlled type 2 diabetes patients relative to age- and BMI-matched controls.76 Thus, in human (pre)diabetes only a few studies have performed combined measurements analysis of cardiac metabolism and function, of which some but not all (depending on the population studied and the methods used) found evidence for the existence of a link between cardiac metabolism and function.

**Therapeutic Options to Improve Myocardial Metabolism in Diabetic Cardiomyopathy**

Since impaired insulin signaling is the key to altered myocardial substrate handling and energy metabolism in type 2 diabetes, it is tempting to propose that the use of insulin or insulin-sensitising therapies will have beneficial effects on cardiac function. Table 2 lists regular blood-glucose-lowering agents and drugs interfering with specific metabolic pathways, their mode of action, non-cardiac metabolic effects and their reported effects on human myocardial metabolism.

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### Table 2: Current Blood-glucose-lowering Agents and Experimental Metabolic Modifiers and Their Effects on Systemic and Cardiac Metabolism

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mode of Action</th>
<th>Systemic/Non-cardiac Effects</th>
<th>Cardiac Metabolic Effects in Humans*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood-glucose-lowering Agents</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biguanides</td>
<td>Partially unknown, activation of AMPK</td>
<td>↑ Insulin sensitivity in liver and skeletal muscle</td>
<td>↓ Myocardial NEFA oxidation ▼ PCr/ATP</td>
</tr>
<tr>
<td>Sulphonylurea derivatives</td>
<td>Blocking of ATP-dependent K⁺-channels</td>
<td>↑ Insulin secretion</td>
<td>↑ Myocardial PCr/ATP</td>
</tr>
<tr>
<td>Insulin</td>
<td>Activation of insulin receptors</td>
<td>↑ Glucose uptake in target organs ↑ Glycogen synthesis in liver ↓ Lipolysis</td>
<td>↑ Myocardial PCr/ATP</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>Activation of PPAR-γ</td>
<td>↑ Insulin sensitivity in liver and muscle</td>
<td>↑ Myocardial PCr/ATP</td>
</tr>
<tr>
<td>GLP-1 receptor agonists</td>
<td>Activation of GLP-1 receptors</td>
<td>↑ Insulin secretion/production ↓ Glucagon secretion ↓ Insulin sensitivity secondary to weight loss</td>
<td>↑ Myocardial PCr/ATP</td>
</tr>
<tr>
<td>DPP-4 inhibitors</td>
<td>Inhibition of DPP-4, preventing degradation of endogenous GLP-1 and GIP</td>
<td>↑ Insulin secretion/production ↓ Glucagon secretion</td>
<td>Not reported</td>
</tr>
<tr>
<td><strong>Metabolic Modifiers</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perhexiline</td>
<td>Inhibition of CPT-1 and 2</td>
<td>▼ NEFA, ↑ glucose metabolism</td>
<td>Not reported</td>
</tr>
<tr>
<td>Trimetazidine/ranazoline</td>
<td>Possibly weak inhibition of CPT-1 or inhibition of LC 3-KAT</td>
<td>▼ NEFA, ↑ glucose metabolism</td>
<td>Not reported</td>
</tr>
<tr>
<td>Etoxymir</td>
<td>Inhibition of CPT-1</td>
<td>▼ NEFA, ↑ glucose metabolism</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

*GLP-receptor agonist-mediated increases in MGI were reported in dogs and rats only. MGI = myocardial glucose uptake; AMPK = AMP-activated protein kinase; NEFA = non-esterified fatty acids; MGT = myocardial triglyceride content; PCr/ATP = phosphocreatinine/adenosine-tri-phosphate ratio; PPAR-γ = peroxisome proliferator-activated receptor-gamma; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like-peptide-1; GIP = glucose-dependent insulinotropic polypeptide; CPT = carnitine-palmitoyl-transferase; LC 3-KAT = long-chain 3-ketoacyl coenzyme A thiolase; ▼ increased; ▼ decreased; ▼ no difference.**
triglyceride content but decreased liver fat content. Pioglitazone combined with insulin for six months, but not insulin alone, reduced myocardial triglyceride content in a small group of patients with long-standing type 2 diabetes, but blood pressure and heart function remained unchanged.141 Furthermore, the association between oxidative stress and cardiac function in human DCM was suggested by the reported association of rosiglitazone-induced reduction of the circulating oxidative stress marker malondialdehyde and therapy-related improvement of LV diastolic function in type 2 diabetes patients without CAD.142 The use of thiazolidinediones has recently been scrutinised because of the elevated risk of CHF. Moreover, rosiglitazone use was associated with cardiac ischaemic events.143 However, this was not observed for pioglitazone.144 Additionally, metformin should be used carefully in those with CHF and renal dysfunction due to the possible increased risk of severe lactic acidosis.145

Novel agents such as the injectable glucagon-like-peptide 1 receptor agonists (GLP-1RA) exenatide and liraglutide and the oral dipeptidyl-peptidase (DPP)-4 inhibitors sitagliptin and vildagliptin are prescribed to lower blood glucose in type 2 diabetes patients. GLP-1RA therapy results in a sustained glycaemic improvement and progressive reduction in bodyweight, which support a shift towards a more favourable cardiovascular risk profile.146 GLP-1RA act through G-protein-coupled receptors, which are also present on cardiomyocytes and raise cyclic AMP.147 Their effect on LV function and metabolism requires further study; however, infusion of GLP-1 improved cardiac function in animals148,149 and patients with CHF.150,151 Recently, the cardioprotective effects of GLP-1 and its metabolite GLP-1(9-36), which is generated by DPP-4 degradation of GLP-1, were demonstrated in a GLP1-/- mouse model.154 Thus, the inotropic effects of GLP-1 and its stimulating actions on glucose uptake, ischaemic preconditioning and vasodilation were shown to be GLP-1-receptor-mediated, whereas the beneficial effects of GLP-1(9-36) on post-ischaemic recovery of cardiac function are compatible with a GLP-1-mediated, whereas the beneficial effects of GLP-1(9-36) on post-ischaemic recovery of cardiac function are compatible with a GLP-1 receptor-independent action.154 To date, there are no data to show effects of DPP-4 inhibitors on the human heart. Since GLP-1RA and DPP-4 inhibitors do not cause fluid retention, hypoglycaemia or lactic acidosis, these drugs may be an important option in the treatment of type 2 diabetes, especially in vulnerable patients with ischaemia or CHF. Large prospective intervention trials in humans applying this novel drug class are eagerly awaited.

Metabolic modifiers such as perhexiline, trimetazidine, ranolazine and etomoxir decrease myocardial FA metabolism and increase glucose metabolism by various different mechanisms (see Table 2).155,156 The antianginal effect of these agents might be directly due to a rise in myocardial efficiency. Recently, three-month treatment with trimetazidine was compared with placebo in type 2 diabetes patients with CAD, and improved LV systolic function and functional capacity despite no change in myocardial perfusion.161 In CHF patients, three months of therapy with etomoxir improved LV function, cardiac output at peak exercise and clinical status.162 However, some concerns exist about the long-lasting safety profile of these metabolic modifiers, which may induce neurotoxicity and/or lipotoxicity (perhexiline) or phospholipodosis (etomoxir).

Conclusion

In experimental DCM, insulin resistance and altered myocardial substrate metabolism lead to glucose lipotoxicity, mitochondrial dysfunction, oxidative stress and altered Ca2+ handling, which adversely affects myocardial contractility. Evidence for myocardial insulin resistance and altered substrate handling to be causal for the observed cardiac functional abnormalities in human DCM remains limited. In selected populations, therapies aimed at improving insulin sensitivity and/or interfering with substrate metabolism have been shown to beneficially affect myocardial function. Further studies in the various stages of human DCM are needed to determine the cardiac metabolic changes and their association to functional alterations over time, in order to establish an evidence based rationale for therapies that target insulin resistance and cardiac metabolism, as well as their appropriate timing in the course of the disease.
Diabetic Gluco-lipotoxic Cardiomyopathy – Amendable by Metabolic Manipulation?