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Nonischemic heart failure in diabetes mellitus

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Abstract

Purpose of review—Diabetic patients with heart failure have a poor prognosis. Although it has been demonstrated in animal models that metabolic maladaptation plays a pivotal role in contractile dysfunction of the heart, the understanding of 'diabetic cardiomyopathy' and its treatment in humans remains incomplete.

Recent findings—Epidemiological studies show that structural changes in the left ventricle can be demonstrated before onset of clinical diabetes. Diastolic dysfunction is the earliest manifestation that is associated with increasing level of serum-free fatty acids and worsening glycemic control. Spectroscopic and histologic evidence in the human myocardium indicates a maladaptive metabolic response in diabetes, characterized by intramyocellular triglyceride accumulation. Studies also suggest a link between myocardial isoform switching, calcium homeostasis and altered metabolism in the development of heart failure. However, treatment directed at deranged metabolic control in diabetes is effective only in animals, and not in humans.

Summary—Although clinical studies suggest the existence of 'diabetic cardiomyopathy', it is still difficult to prove causality. However, animal models and human studies suggest that systemic metabolic derangements may lead to metabolic, functional and structural maladaptation of the heart. The exact mechanisms of heart failure in diabetes remain elusive.

Keywords

adaptation; diabetes mellitus; heart failure; substrate metabolism

Introduction

Nonischemic heart failure in diabetes mellitus has been recognized by clinicians for more than a century. Not too long after Minkowski's [1,2] classic experiments on the cause of diabetes mellitus, it was already speculated that heart disease in diabetes can be traced to an abnormality in intermediary metabolism. Whereas heart failure is primarily a disease of contractile dysfunction of the heart and diabetes mellitus is primarily a systemic disease of metabolic dysregulation, it is becoming increasingly apparent that both diseases are interrelated [3]. Similar to heart failure, diabetes mellitus is a growing problem with prevalence increasing steadily from 2.9% in 1974 to 4.7% in 1998 and is estimated to reach 5.5% in 2025 [4•]. Epidemiological studies [4•] have shown that patients with diabetes also suffer from cardiovascular diseases, and that the population attributable risk for

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cardiovascular diseases is increasing. In addition, patients with diabetes mellitus, especially women, are at a high risk for developing heart failure [5]. Nonischemic cardiomyopathy in the form of diabetic cardiomyopathy (DCM) forms a large part of the problem.

Background

The existence of a DCM was first proposed in epidemiological and experimental studies documenting structural and functional changes of the heart. However, the term suffers from poor definition. As established by Koch [6] at the end of the 19th century, a cause and effect relationship must exist between a given factor and the disease. It is difficult to apply the principle of Koch's postulates for a causative link between diabetes mellitus and a specific cardiomyopathy causing heart failure. This difficulty stems partly from the fact that natural history is interrupted by the treatment, and that most patients are already receiving antidiabetic medications by the time they present with overt heart failure. Also, the effect of excess insulin in the insulin-resistant state leading to accelerated atherosclerosis and endothelial dysfunction contributing to heart failure further complicates the issue [3]. Finally, the presence of myocardial metabolic changes before there are any functional changes and the development of diastolic dysfunction in the heart before the onset of symptoms make DCM difficult to define. It is not clear whether DCM is a cause or a consequence of insulin resistance [7]. We have speculated that metabolic dysregulation in the body as a whole and impaired metabolic flexibility in the heart precede, trigger and sustain functional and structural changes [8].

Here we discuss the newer epidemiological data on heart failure in diabetic patients, new data for suggested mechanisms of DCM in humans, and advances in the early detection as well as in the treatment of DCM. There are several excellent reviews of established concepts in DCM from animal models, and we wish to direct the reader to them for further details on the potential molecular mechanisms that link diabetes mellitus and heart failure [9,10••,11].

Metabolic concepts and hypotheses

The pathogenesis of heart failure in diabetic patients is multifactorial and includes not only the metabolic changes of insulin resistance (high blood levels of glucose, fatty acids, and insulin) but also the increased fibrosis and cardiomyocyte apoptosis driven by increased inflammation and over activity of the renin–angiotensin system [12].

Metabolic dysregulation in diabetes mellitus involves both glucose and fatty acid metabolism [13]. We have earlier proposed a model of adaptation and maladaptation of the heart in response to the altered metabolism [3,14]. A prominent feature is that the cardiac myocyte returns to the fetal gene program leading to an increase in the expression of myosin heavy chain beta (MHCβ) and a decrease in the expression of adult isoform MHCα [15,16]. We have postulated that a decrease in glucose oxidation causes an accumulation of glycolytic intermediates that decreases the sarcoplasmic reticulum calcium ATPase 2a (SERCA2a) expression, an essential enzyme in calcium homeostasis, and leads to a diastolic dysfunction, frequently observed in DCM. Moreover, we have recently identified glucose-6-phosphate, the first intermediate in the glycolytic pathway, to be an intracellular signaling molecule that regulates protein synthesis in cardiomyocytes through mammalian target of rapamycin (mTOR) activation. This adds strength to our hypothesis of metabolic regulation of cardiac hypertrophy in diabetic patients [17].

The metabolic adaptation in the form of activation of fatty acid metabolizing pathways through the nuclear receptor peroxisome proliferator activated receptor-α (PPARα) activation and the inhibition of glucose utilization pathways through the inhibition of the pyruvate dehydrogenase complex (PDC) and phosphofructokinase results in the use of fatty

acid as a preferential, albeit relatively inefficient, fuel. In the diabetic heart, increased fatty acid oxidation is suspected to promote mitochondrial uncoupling, a mechanism that may contribute to diminished myocardial high-energy reserves and contractile dysfunction [18].

Several years ago we postulated that the accumulation of glucose and fatty acid metabolites results in complex consequences finally leading to lipotoxicity, glucotoxicity, or glucolipotoxicity [14]. Glucotoxicity and lipotoxicity are associated with advanced glycosylation end-product (AGE) deposition and ceramide formation, which leads to reactive oxygen species (ROS) generation [19,20]. ROS, in turn, affect intracellular homeostasis, Ca^{2+} cycling, mitochondrial function and programmed cell death [21,22]. Several advances have been made since our earlier reviews of the subject.

Newer epidemiological evidence

In the Framingham Heart Study population, the diagnosis of diabetes decreased the lifespan by 8.2 years in women and 7.5 years in men [23]. Similar decreasing survival was seen in patients with heart failure. In a retrospective cohort study of 665 heart failure patients from the Mayo Clinic, Rochester, the presence of diabetes decreased the 5-year survival from 46 to 37% ($P = 0.017$) after adjustment for covariates [24] (Fig. 1). Although none of these studies has identified DCM as a cause of premature death and disability in diabetic patients, it appears that diabetes adversely affects the life expectancy in the general population and also in patients with heart failure. It also raises the question of whether insulin resistance is associated with heart failure.

Early heart disease and diastolic dysfunction in diabetes

The effects of insulin resistance on the heart are seen even before the onset of clinical diabetes. In an analysis of 2623 patients in the Framingham Study [25], left ventricular mass increased across categories of worsening glucose tolerance even when adjusted for BMI and blood pressure. The effect was more prominent in women ($P < 0.001$) than in men ($P = 0.054$). Similar gender differences have been reported in the Strong Heart Study [26].

The earliest functional abnormality in DCM is impaired diastolic function. Decrease in the rate of early diastolic filling, decreased early-to-late velocity ratio, and a prolongation of isovolumetric relaxation are the most popular features to diagnose diastolic dysfunction by echocardiography [27]. In nondiabetic obese patients, there is an inverse relation between serum free fatty acid levels and diastolic function as assessed by tissue Doppler imaging [28,29]. In a study of 25 type 1 diabetic patients [30], the severity of diastolic dysfunction correlated well with hemoglobin A1c levels (correlation coefficient $r = 0.68$; $P = 0.0002$). Clinical examination or serum markers such as brain natriuretic peptide level are not useful to diagnose diastolic dysfunction in DCM [31]. Recent studies in diabetic patients indicate that early detection of myocardial dysfunction is also possible by using exercise Doppler echocardiography. In contrast to resting mitral annular and inflow velocities, diastolic and systolic velocities during exercise in type 2 diabetic patients are substantially reduced [32]. Hence, early detection of diastolic dysfunction may be possible by the assessment of left ventricular (LV) functional reserve over time.

Links between metabolic dysregulation and diabetic cardiomyopathy in humans

A link between myocardial dysfunction in DCM, lipo-toxicity and glucotoxicity has been proposed in animal models. Recent studies [33,34•] using myocardial biopsy specimens *ex vivo* as well as advanced imaging techniques with proton MRI spectroscopy *in vivo*

extended these hypotheses to the human heart. Although all the pathways from initial insult to the development of DCM are not fully understood, these studies form the framework of a jigsaw puzzle yet to be completed. New imaging techniques raise the hope that in the future, molecular imaging may help diagnose DCM earlier than it is possible today and to follow the results of pharmacological interventions. The studies reviewed for the purpose of this article are listed in Table 1

Altered cardiac metabolism in diabetes

The initial changes of cardiac energy substrate metabolism in diabetes are an increase in fatty acid oxidation and a decrease in glucose oxidation. This metabolic shift was first described by Randle *et al.* [35] in normal perfused rat hearts. Recently the same metabolic shift has also been demonstrated in the hearts of a cohort of 11 patients with type 1 diabetes using PET [36]. Although the plasma insulin, lactate level and myocardial blood flow were similar to those in the controls, in diabetic patients the heart exhibited higher rates of fatty acid oxidation and utilization. At the same time, the rate of glucose oxidation decreased [36].

Our laboratory reported an upregulation of PPARα-regulated genes in patients with diabetes and high BMI who presented with nonischemic cardiomyopathy [33,37]. PPARα is a key regulator of enzymes of fatty acid oxidation, which suggests that in diabetic patients there is an increase in fatty acid oxidation as a result of metabolic adaptation due to the increased fatty acid supply to the heart [33].

Epicardial adipose tissue

In the heart, epicardial adipose tissue (EAT) covers 80% of its surface and constitutes approximately 20% of the total heart weight [38•]. Adipose tissue is an organ with both endocrine and paracrine properties that are actively involved in crosstalk with muscle tissue [39]. The exchange of hormones and metabolic mediators has been implicated in the induction of insulin resistance in skeletal muscle cells [39]. It is reasonable to speculate that the fat surrounding the heart plays a role in insulin sensitivity and function of the cardiomyocyte [40•]. One indication of its effect on insulin resistance is EAT's low levels of lipoprotein lipase [41] that has been associated with insulin resistance in the metabolic syndrome [42]. Moreover, given the shared embryonic origins of EAT and visceral adipose tissue and its close proximity to the coronary vessels and access to the myocardium [43], there is a good possibility that excess EAT may contribute to cardiac dysfunction, much in the same way as excess visceral adipose tissue does so in hepatic steatosis. Furthermore, the crosstalk between EAT and the myocardium is facilitated by the lack of a fascia layer that would otherwise impede the diffusion of metabolites [43]. This creates contiguity between the two tissues and may facilitate the development of insulin resistance and cardiac dysfunction in excess EAT. In general, our understanding of EAT is still limited. Given the biochemical and physiological differences between the fat depots in the body, the time is ripe to elucidate what role EAT may play in insulin sensitivity and cardiac function.

Myosin heavy chain isoform switching

Part of adaptation of the myocardium to stressor involves the switching of the MHC isoform from alpha to beta, and this response is augmented by diabetes. We have postulated a role for the hexosamine biosynthetic pathway (*N*-acetyl-glucosamine) in the regulation of the fetal isoform switch [44]. The hypothesis was based on the analysis of transcripts of myocyte enhancer factor 2C (MEF2C), glucose transporter (GLUT4) and MHCα in failing human hearts of diabetic patients compared with nonfailing hearts of nondiabetic patients [45].

Altered calcium homeostasis

Diastolic dysfunction is the earliest feature of contractile abnormality in diabetic patients. Dysregulation of calcium homeostasis has been implicated in this in animal models [3]. In a study of human cardiac myocytes from patients with T2DM, confirmation of calcium dysregulation was seen. Jweied *et al.* [46] demonstrated a decreased cardiac myofilament responsiveness to calcium as shown by decreased calcium sensitivity and a trend toward a reduction in maximum Ca^{2+}-saturated force generation.

SERCA2a is a key regulator of intracellular calcium levels. Our laboratory demonstrated that in failing diabetic hearts, SERCA2a transcripts were decreased along with other transcripts that were regulated by glucose. This confirmed the findings in mouse models, which indicate that intermediates of glucose metabolism play a role in calcium homeostasis [45].

Lipotoxicity in heart muscle

Maladaptation in the heart results in lipid accumulation in mouse models of diabetes [33]. In the human heart, cardiac steatosis seems to precede the development of contractile dysfunction [34•]. Using localized ^{1}H magnetic resonance spectroscopy (MRS) and cardiac MRI to measure myocardial triglyceride content and LV function, the investigators compared lean patients, obese patients, patients with impaired glucose tolerance and T2DM. Myocardial triglyceride content increased as the insulin resistance increased despite LV ejection fraction remaining normal and comparable across all groups. This suggests that steatosis precedes the full-blown picture of DCM and plays an important role in its pathogenesis [34•].

Mitochondrial dysfunction

The main pathways of energy substrate metabolism provide the electromotive force that drives the oxidative phosphorylation of ADP. Hence, it is easily deducible that mitochondrial dysfunction would be seen in DCM. Mitochondrial function in humans has been studied using ^{31}P nuclear MRS. The phosphocreatinine (PCr)/ATP ratio has been used as a surrogate marker for mitochondrial function in the human myocardium [47,48]. Using these criteria, a decrease in the PCr/ATP ratio and PCr by half has been observed in the hearts of patients with T2DM [49].

In a study [50] of 12 newly diagnosed, well controlled patients with type 2 diabetes and 12 nondiabetic subjects, diastolic dysfunction, LV mass and high energy phosphate metabolism were studied simultaneously. The investigators found diastolic dysfunction in the absence of increased LV mass or systolic dysfunction independent of age and blood pressure. Diastolic dysfunction is associated with a lower PCr/ATP ratio [50]. Although these studies have demonstrated mitochondrial dysfunction in DCM, it is still not proven whether the dysfunction is a cause or effect of DCM.

Protein glycosylation and advanced glycation end products

The stiffness in the myocardium leading to diastolic dysfunction has also been attributed to the deposition of advanced glycation end (AGE) products. It was observed already some time ago that the serum levels of AGE products correlated with diastolic dysfunction [51]. An increased flux of glucose carbon through the hexosamine biosynthetic pathway in the heart muscle cell may be responsible for UDP-*N*-acetylglucosamine (*O*-GlcNAc) acylation [52•]. There is good experimental evidence that an increase of *O*-GlcNAc on specific proteins may contribute to impaired cardiomyocyte function in the Zucker diabetic fatty rat [53•]. Recently, it was demonstrated that the human myocardium in patients with diabetes had a greater deposition of AGE products, especially in patients with reduced ejection

fraction. However, the myocytes from diabetes mellitus patients with intact ejection fraction had decreased contractility [54]. Thus, the role of AGE in the modulation of contractile performance of the heart still needs to be defined.

Therapeutic interventions

On the basis of deranged pathophysiology outlined above, interventions to prevent or treat DCM have been directed toward prevention of further insults of insulin resistance, hyperglycemia and increased plasma fatty acid levels and disruption of the subsequent metabolic pathways that are upregulated in response to the increased load.

The first goal can be achieved by the use of traditional glucose-lowering regimens including insulin and insulin-sensitizing agents. The second goal is harder to achieve, but it is exciting because of newer pharmaceutical targets. In the following sections we present animal and human data regarding clinically relevant interventions. The most important studies are summarized in Table 2.

Insulin

Insulin is an inotropic agent that lowers systemic vascular resistance [55] and increases hemodynamic performance in both normal and diabetic patients. However, the increase in the LV ejection fraction is less pronounced in diabetic than in nondiabetic patients [56]. Also, the increases in LV function may not translate into survival benefit in patients with heart failure. In a systematic review of four trials, the effect of insulin on mortality in diabetic patients with heart failure was conflicting. In the three smaller studies that compared the use of insulin to insulin secretagogues and insulin sensitizers, insulin use was associated with increased unadjusted all-cause mortality. However, in a large study of 8187 patients [57], adjusted all-cause mortality was not increased. Because all these studies were not randomized control trials comparing insulin with other treatment regimens, it is hard to determine the exact effect of insulin on long-term outcomes in diabetic patients with heart failure.

Metformin

Metformin is also an insulin sensitizer in the peripheral tissues. Although the precise mechanism is not known, it is hypothesized that metformin improves metabolism by activating AMP-activated protein kinase (AMPK) in several tissues [58]. Whereas the drug inhibits hepatic gluconeogenesis [59], recent in-vitro studies [60] have suggested that the activation of AMPK may also promote glucose uptake. However, MRS studies in the human myocardium [61] have shown that there was no increase in the myocardial glucose uptake when compared with placebo. Metformin has also been seen to alleviate lipo-toxicity in cultured myocytes by promoting fatty acid oxidation and subsequently decreasing ceramide levels [62]. Although it remains to be shown in humans, metformin may also inhibit cardiac hypertrophy through AMPK-mediated inhibition of protein synthesis [63]. Traditionally, metformin has not been used in the patients with heart failure because of concerns of lactic acidosis. In a recent systematic review [57], use of metformin in type 2 diabetes patients with heart failure was not associated with harm, and these patients did not have increased admissions for heart failure. But the role of metformin in improving function and cardiac performance in DCM is currently unknown.

Thiazolidinediones

Thiazolidinediones (TZDs) improve insulin sensitivity by lowering plasma-free fatty acids levels and modulating transcription of metabolic enzymes through the activation of the

PPARγ receptor [64–66]. Experimental studies on myocardial effects of TZDs have shed light on the various pathways regulating insulin responsiveness. In animal studies [67], rosiglitazone was shown to increase the concentrations of glucose transporters 1 and 4 and to improve myocardial glucose uptake. In Zucker diabetic rats, TZDs lower myocardial triglyceride and ceramides content and prevent loss of cardiac function [68]. Similar effects including increased rates of myocardial glucose oxidation were observed with a non-TZD compound [69]. An intriguing finding is that in patients on TZD pioglitazone, decreased myocardial triglyceride levels ($P = 0.02$) have been observed, when compared with insulin [70]. A recent study [71] of the rat ventricular myocytes also found that rosiglitazone upregulates adiponectin receptors in the myocardium, which in turn increases fatty acid oxidation and glucose uptake in the myocardium. In humans, rosiglitazone improves insulin-stimulated myocardial glucose uptake when assessed by fluorodeoxy-D-glucose (FDG) and PET scanning in patients with T2DM [61]. Similar findings were seen even in the myocardium of type 2 diabetes patients with coronary artery disease [72]. These changes in the myocardial metabolism by rosiglitazone are reflected in the improvement of myocardial function.

Both pioglitazone and troglitazone have been shown to improve LV diastolic function without affecting LV mass in hypertensive patients and in patients with T2DM [73,74]. Although all these studies provide a strong biological basis for TZDs being beneficial in heart failure, the long-term follow-up of patients with diabetes taking TZDs has revealed a higher risk of heart failure. This is primarily related to TZD-related fluid retention [75]. Even though the exact mechanism of fluid retention remains unknown, it is considered to be noncardiac in origin. This led to American Diabetes Association/American Heart Association (ADA/AHA) guidelines restricting the use of TZDs in patients with class III and IV heart failure [75]. In a recent meta-analysis of seven randomized control trials (RCTs), TZDs (either pioglitazone or rosiglitazone) increased the risk of development of heart failure [relative risk 1.72; 95% confidence interval (CI) 1.21–2.42; $P = 0.002$] in patients with type 2 diabetes and prediabetes when compared with controls. However, it did not increase the risk of cardiovascular mortality suggesting that the heart failure that develops with TZD use may be different from heart failure that develops due to systolic or diastolic dysfunction [76]. Similar results of increased risk for heart failure without an increase in mortality were reported from another meta-analysis of 19 RCTs of pioglitazone use in type 2 diabetes [77].

In a systematic review of eight studies comparing different antidiabetic agents in patients with heart failure, TZDs were associated with increased admission for heart failure [pooled odds ratio (OR) 1.13; 95% CI 1.04–1.22; $P = 0.004$]. However, TZDs were associated with a decreased all-cause mortality (pooled OR 0.83; 95% CI 0.71–0.97; $P = 0.02$) [57]. In the light of the new data that TZDs do not increase mortality despite increasing heart failure, we can speculate that TZDs may unmask a previously existing dysfunction by causing volume overload, and as long as the heart failure is managed with appropriate therapy, it may have survival benefit in type 2 diabetes patients. The use of TZDs in diabetic patients is also associated with an increased risk of myocardial infarction without a significant increase in death from cardiovascular causes according to a recent meta-analysis by Nissen and Wolski [78](OR = 1.43;95%CI = 1.03–1.98; $P = 0.03$). This may further limit the use of TZDs in diabetic patients and highlights the complex nature of metabolic modulation.

Glucagon-like peptide 1

Glucagon like peptide 1 (GLP-1) is an incretin hormone that promotes insulin secretion in response to glucose. GLP-1 has been shown to have direct protective effect on the myocardium directly acting via the GLP-1 receptor. Infusion of GLP-1 has been shown to improve LV ejection fraction in patients with acute myocardial infarction and heart failure

[78,79]. Although no effect on DCM has been studied, GLP-1 appears to be an exciting new drug for DCM as it affects glucose metabolism.

Conclusion

DCM remains a disease without a proper definition. Attempts to characterize the pathogenesis of DCM in humans have been aided by animal models. Mitochondrial dysfunction with related ROS production seems to be one of the major pathways for myocardial injury. Newer imaging techniques, including PET and MRS, have added powerful tools to assess dysregulated myocardial metabolism *in vivo*, although it is still elusive whether insulin resistance and diabetes are a cause or a consequence of heart failure. It is hoped that ongoing research will lead to the identification of new intracellular targets for identifying patients with diabetes at risk of developing heart failure.

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

• of special interest

•• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 288).

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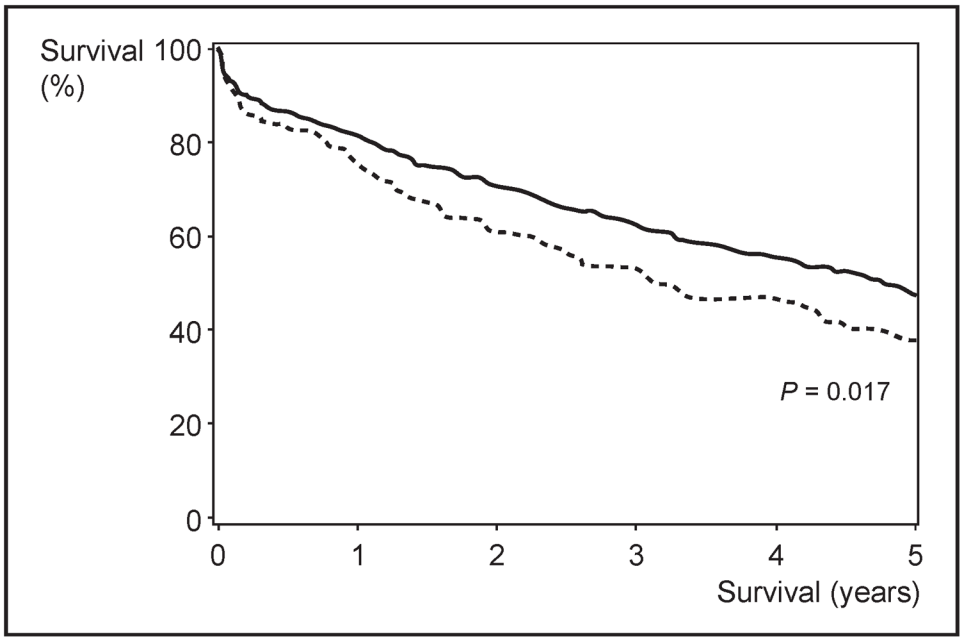

Figure 1. Kaplan–Meier survival curve of two cohorts of patients with heart failure
The survival is less in patients with diabetes mellitus. Adapted with permission [24].

Table 1

Potential mechanisms linking metabolism, energy transfer, calcium homeostasis and contractile function in the heart of patients with DCM

Topic and reference of the study	Population studied	Investigative technique	Finding
Altered myocardial metabolism			
Herrero *et al.* [36]	T1DM	PET	Increased glucose and fatty acids oxidation
Sharma *et al.* [33]	T2DM	qPCR	Increased PPARα expression
Lipotoxicity			
Sharma *et al.* [33]	T2DM	Histology	Increased myocardial lipid deposition
McGavock *et al.* [34•]	T2DM	MRS	Increased myocardial triglyceride content
Glucotoxicity			
van Heerebeek *et al.* [54]	T1DM, T2DM	Immunostaining	Increased AGE deposition (mainly in the wall of small heart vessels)
Impaired energy transfer			
Diamant *et al.* [50]	T2DM	MRS/MRI	Decreased PCr/ATP ratio
Impaired calcium homeostasis			
Jweied *et al.* [46]	T2DM	Electro-physiology	Decreased cardiac myofilament Ca^{2+} responsiveness and maximum Ca^{2+}-saturated force-development
Razeghi *et al.* [45]	T2DM	qPCR	Decreased SERCA2a expression
Altered contractile function			
Razeghi *et al.* [45]	T2DM	qPCR	Decreased MHCα expression
Sharma *et al.* [33]	T2DM	qPCR	Increased MHCβ expression

AGE, advanced glycation end products; DCM, diabetic cardiomyopathy; MHC, myosin heavy chain; MRS, magnetic resonance spectroscopy; PET, positron emission tomography; PCr, phosphocreatine; PPARα, peroxisome proliferator activated receptor-α; qPCR, real-time polymerase chain reaction; SERCA2a, sarcoplasmic reticulum Ca^{2+} ATPase; T1DM/T2DM, type 1/type 2 diabetes mellitus.

Table 2

Metabolic interventions in the treatment of diabetic cardiomyopathy

Therapy	Mechanism of action	Benefit	Disadvantages/risk
Insulin	Improves glucose uptake and utilization, contributes to normalize plasma lipids levels	Improves LVEF [56]	Undetermined increased mortality in patients with diabetes mellitus and HF [57]
Thiazolidinediones	Lower plasma lipids levels, increases fatty acids oxidation, improves glucose uptake	Improves LVEF [73,74]	Increased risk of edema [75] without HF increased mortality [76,77]
Metformin	Decreases hepatic glucose production, increases insulin action in muscle and fat, activates AMPK	Insufficient data	Insufficient data
GLP-1 inhibitors	Increases secretion of insulin, direct effect on myocardium	Improves LVEF [79]	Short duration of action requires continuous infusion

AMPK, AMP-activated protein kinase; GLP-1, glucagon-like peptide 1; HF, heart failure; LVEF, left ventricular ejection fraction.