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The Complexity of Diabetic Cardiomyopathy: Lessons from Patients and Animal Models

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Abstract

Cardiovascular diseases are foreseeable complications of diabetes mellitus. Prominent among those complications is heart failure. Diabetic cardiomyopathy is a distinct entity independent of coronary artery disease and hypertension. Most of our knowledge on the pathogenesis of diabetic cardiomyopathy comes from studies performed on various animal models. The recent advances in the domain confirm that the disease is above all a maladaptation of the heart mostly driven by the metabolic derangements that accompany diabetes mellitus.

Introduction

Diabetes mellitus is considered one of the major causes of premature death and disability, mainly due to cardiovascular complications. With the depressing forecast of 366 millions people suffering from diabetes by 2030, the epidemic represents a sword of Damocles for health care in most countries [1]. The increasing prevalence of obesity is considered a “firestarter” for type 2 diabetes.

Prominent among the complications of diabetes is heart failure. Diabetic cardiomyopathy (DCM) was historically described as a disease process that affects the myocardium independently of macrovascular complications currently associated with common risk factors like arterial hypertension, hypercholesterolemia, and coronary artery disease [2]. Although many of the structural and functional abnormalities of the heart which characterize DCM have been described, the origins of the disease are still unclear. The pathogenesis of DCM is an active field of investigation, and we wish to refer the reader to other excellent reviews published recently on the matter [3–5]. We report here recent advances in research supporting the idea that DCM may originate from a failure of the heart to adapt to chronic changes in cardiac metabolism.

Evidence for Diabetic Cardiomyopathy in Humans

Structural and functional features of diabetic cardiomyopathy

In the 1970s the Framingham Heart Study demonstrated an increased incidence of congestive heart failure in diabetic patients of both sexes, which was independent of age, obesity, hypertension, coronary artery disease, and hypercholesterolemia [6]. Echocardiographic studies on independent populations and the more recent use of transmitral inflow with tissue Doppler analysis have permitted to establish the typical pattern of alterations characterizing DCM [7]. Diabetic cardiomyopathy is a combination of

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left ventricular structure abnormalities (concentric remodeling/hypertrophy) with diastolic dysfunction, which may precede the development of systolic dysfunction and eventually progress to overt heart failure. Heart failure is defined as a clinical syndrome in which exercise intolerance is associated with left ventricular (LV) dysfunction of the heart [8].

Systemic and myocardial metabolic shifts

When considering heart failure in patients with diabetes one must also consider the metabolic derangements of diabetes mellitus: hyperglycemia, insulin resistance (for type 2 diabetes), and dyslipidemia with increased levels of circulating nonesterified fatty acids (NEFA). The resulting changes in nutrient supply and uptake at the level of the cardiac myocyte dramatically affect the way the heart converts chemical to mechanical energy. Exact mechanisms still need to be worked out. According to the studies performed in animal models, a main feature of DCM is intramyocardial lipid accumulation [3–5], and the concept of cardiac lipotoxicity will be discussed further below. While cardiac steatosis was already considered as a possible cause of sudden death during the nineteenth century [9], both its presence and its involvement in the development of DCM in humans have been ignored for a long time.

We have observed intramyocardial lipid accumulation in the failing heart of diabetic patients that resembles the lipotoxic Zucker diabetic fatty (ZDF) rat heart [10]. More recent work by others has shown that cardiac steatosis is found in patients with impaired glucose tolerance and precedes the onset of type 2 diabetes mellitus and LV systolic dysfunction [11]. Intramyocardial lipid accumulation in type 2 diabetic patients directly also correlates with impaired contractility and decreased capability of myocytes to adapt following infarction [12]. Both increased plasma NEFA levels and myocardial triglyceride accumulation are correlated to impaired diastolic function in healthy young people [13]. Lastly, abnormal left ventricular energy metabolism in obese insulin resistant men precedes functional and structural remodeling of the heart [14]. Thus a metabolic derangement of the heart characterized by an intramyocardial lipid accumulation is likely to contribute to DCM development in humans.

The Pathogenesis of Diabetic Cardiomyopathy

Animal models of diabetic cardiomyopathy

Most of the molecular mechanisms involved in the pathogenesis of DCM have been (and are) investigated with rodent animal models of type 1 or type 2 diabetes mellitus (see Table). Because DCM is a complex multifactorial disease, it is unlikely that there will ever be an animal model which presents all the various aspects of the human syndrome. The mechanisms of the disease are therefore investigated separately in a wide spectrum of different models [15]. The models consist either of animals with defective insulin actions or signaling, with an altered cardiac glucose and/or fatty acid utilization, with enhanced oxidative stress, or with enhanced cardiac fibrosis. The most popular animal models include the chemical ablation of the β cells of the pancreas (Streptozotocin (STZ)-treated rodents), animals spontaneously deficient in the leptin signaling (ob/ob and db/db mice, ZDF rats), and transgenic animals with a cardiac-specific lipotoxicity. All these models are not without limitations. In contrast to humans with diabetes mellitus, rodents are resistant to the development of atherosclerotic lesions and ischemia. At the same time animals unlike human patients are often not treated for diabetes. The rodent models have nonetheless served to identify a number of defects which are likely to be responsible for the development of DCM in humans. Recent studies using broad transcriptomic or proteomic approaches give a good overview of the profound modifications that affect the heart in diabetes mellitus [16; 17]. Besides the dysregulation of circulating factors which contributes to heart fibrosis and

hypertrophy, the major intramyocellular changes focus on cardiac metabolism and a subsequent series of defects in mitochondrial function, reactive oxygen species (ROS) generation or dissipation, and in calcium homeostasis.

Circulating factors, apoptosis and cardiac fibrosis

Impaired contractile function seems to be partly caused by cell necrosis or apoptosis and myocardial fibrosis, although a recent study using noninvasive echocardiography and invasive LV catheterization rather reported a reduction of LV mass in STZ-treated rats [18]. Several circulating factors have been shown to trigger the myocardial remodeling and constitute potential therapeutic targets for treating DCM. Thus, the upregulation of the renin-angiotensin system in the diabetic heart enhances oxidative stress and myocardial cell death [19], and its blockade attenuates myofibrillar remodeling in the heart [20]. The deleterious effects of hyperglycemia on advanced glycated end products (AGEs) receptor activation and increase of intracardiac profibrogenic factors are alleviated by dehydroepiandrosterone (DHEA) treatment [21]. Leukocyte infiltration of the heart is also likely to play a pivotal role in the pathophysiology of DCM, and both, treatment with Pralnacasan and Atorvastatin, aiming to decrease intramyocardial inflammation, improved cardiac function in STZ-treated rats [22; 23].

Cardiac metabolism

In metabolic terms the mammalian heart is an omnivore which burns both fatty acids and glucose. Under normal conditions, 60% to 90% of the cardiac ATP comes from oxidative phosphorylation of ADP and oxidation of fatty acids [24]. However, cardioprotective innate mechanisms in normal heart include an increase of carbohydrate oxidation in acute and chronic stress conditions like ischemia or hypertrophy [25]. But in the diabetic state, the heart relies essentially on fatty acid oxidation for energy provision, even under stress [26]. The enhanced fatty acid metabolism may be the consequence of the Randle's "glucose fatty-acid cycle" [27], which stresses the inhibition of glucose oxidation by fatty acids to a greater extent than glycolysis and the inhibition of glycolysis to a greater extent than glucose uptake, but it may be also due to a decrease in glucose uptake triggered by insulin resistance. Thus, the metabolic flexibility of the heart is impaired with diabetes, which we consider a major contributing factor to cardiac maladaptation [28].

The most common perception on cardiac metabolism in diabetes mellitus is that NEFA supply is overwhelming the oxidative capacities of the heart, therefore leading to the intrasarcoplasmic accumulation of neutral lipids and their intermediates. The excess of lipid intermediates is then directed to signaling pathways whose overactivity will affect critical mechanisms like ATP production, insulin sensitivity, cell contractility, and apoptosis. In short, DCM is a lipotoxic cardiomyopathy. Thus, ceramide is a multifunctional regulatory molecule, at the crossroads of the inflammatory response, insulin resistance, and apoptosis [29]. Diacylglycerol induces insulin resistance by activating distinct isoforms of protein kinase C [30]. The long-chain fatty acyl CoA themselves can inhibit glycolysis and are suspected to regulate glucose uptake [31]. Excess palmitoyl-CoA is also suspected to trigger intrinsic apoptosis by enhancing endoplasmic reticulum stress and calcium release [32].

Although several checkpoints regulate fatty acid metabolism, recent results have stressed the importance of fatty acid uptake in the regulation of intramyocardial lipid content. Cardiomyocytes from rats fed a high fat diet for 8 weeks display an increased localization of the fatty acid translocase FAT/CD36 at the sarcolemma, which is preceding the onset of cardiac contractile dysfunction [33]. Moreover, CD36 deficiency is sufficient to reverse the lipotoxic phenotype of mice with cardiac-specific overexpression of the nuclear receptor PPARα [34].

While much emphasis has been given to the lipotoxic aspect of DCM, dysregulated carbohydrate metabolism and glucotoxicity must also be considered. Hyperglycemia and insulin resistance are further contributors to cardiac maladaptation in the diabetic state. According to the Randle hypothesis, glucose may accumulate into the cells and be redirected to alternate metabolic pathways with additional regulatory consequences, namely the pentose phosphate pathway and the hexosamine biosynthetic pathway [35]. For example, increased intracellular levels of UDP-N-acetylglucosamine is suspected to alter excitation/contraction coupling by promoting the O-linked glycosylation of target proteins like the myosin heavy chain (MHC) isoforms or the sarcoplasmic/endoplasmic reticulum Ca^{2+}-ATPase (SERCA). Accordingly, impaired cardiomyocyte function in ZDF rats is associated with an increase in O-linked glycosylation of high-molecular-mass proteins [36]. Moreover, hyperglycemia is likely to be responsible for the decrease in protein levels of the essential myocardial survival factor GATA4 seen in several animal models of diabetes mellitus [37]. The expression levels of the glucose transporters GLUT1 and GLUT4 are downregulated quickly and in a sustained manner after the onset of insulin-deficient diabetes, possibly as an adaptative mechanism of the heart [38]. Given the deleterious effects of hyperglycemia, it is tempting to consider the hypothesis arguing that insulin resistance may be, at least on the short term, a physiological mechanism to protect the cell [39]. It should be noted that unlike PPARα, cardiac-specific overexpression of PPARβ/δ does not induce lipotoxic cardiomyopathy. In fact, while both nuclear receptors induce expression of genes involved in mitochondrial fatty acid oxidation, PPARβ/δ preferentially induces glucose utilization whereas PPARα represses it [40].

In short, DCM is primarily a metabolic cardiomyopathy. Defects in both fatty acid and glucose oxidation pathways are intimately related and are preceding the contractile dysfunctions.

Impaired mitochondrial function

Because the mitochondrion is the cradle of both glucose and fatty acids conversion to a usable form of energy (ATP), it was obvious to hypothesize that the impaired metabolism characterizing DCM may be related to mitochondrial dysfunction. Not surprisingly, impaired mitochondrial function has been demonstrated in type 1 and type 2 diabetic animals. Microarray analysis performed on the LV transcriptome of STZ-treated rats revealed that a disproportionate number of the genes whose expression is significantly altered by diabetes are expressed in the mitochondrion [16]. Most of these genes encode for enzymes involved in β oxidation and are highly upregulated in accordance to the switch toward fatty acid utilization. There is also an increased number of mitochondria in cardiomyocytes of type 1 and type 2 models of diabetes [41; 42], which is probably due to the activation of mitochondrial biogenesis by the coactivator of PPARα, PGC-1α. However, the genes encoding for several components of the oxidative phosphorylation process (the “OXPHOS proteins”) are rather downregulated [43]. Lastly, ATP production in the diabetic heart is decreased. Therefore, the increase in mitochondrial number and volume density does not compensate for the decrease in energy coupling.

The mitochondrion is also a central determinant of cell survival. The mitochondrion forms a converging node for apoptotic stimuli by promoting the release of pro-apoptotic factors like cytochrome c, Smac/DIABLO, and the apoptosis-inducing factor (AIF). This intrinsic pathway of apoptosis is overactivated in the heart of ZDF rats and may be involved in remodeling and cardiac dysfunction [44]. Moreover the loss of cardiolipin, an important component of the inner mitochondrial membrane necessary for oxidative phosphorylation, is an early event related to apoptosis in animal models of diabetes [45]. The mitochondrion is also an important source of ROS, which are a naturally-occurring byproduct of the respiratory process. ROS production is enhanced in the diabetic heart consequently to the

increased reliance of the cells on β oxidation. Recent data support the activation of a fatty acid-mediated uncoupling system in the mitochondrion that may help to dissipate this oxidative stress. Evidences point toward the activation of a long-chain fatty acyl CoA generation and export system in the mitochondria of STZ-induced diabetic rats [46]. We have found that such a mechanism was activated in rats fed a high fat diet for 48 weeks and correlated to a maintained cardiac power, whereas rats fed a high carbohydrate and high fat diet (Western diet) did not show any activation of this system and elicited impaired cardiac function [47]. However, others think that uncoupling mechanisms may be detrimental on the long term by driving an ATP depletion [48]. Whether the fatty acid-mediated uncoupling system is beneficial or not in DCM will require further investigations. However, the chronic activation of this system may partly explain why the heart maladapts in diabetes mellitus.

Reactive oxygen species and oxidative stress

Oxidative stress in DCM may be caused by an increase in ROS production and a concomitant decrease in the antioxidant defenses of the cell [17]. Strategies that enhance mitochondrial ROS scavenging systems allow to reduce diabetes-induced cardiac dysfunction [4]. Even thought the respiratory chain of the mitochondrion is a primary source for ROS production in the diabetic cardiomyocyte [49], ROS can also be generated by other enzymatic systems, such as NADPH oxidase whose expression is increased by hyperglycemia, or xanthine oxidoreductase [50; 51]. ROS may be involved in the cardiac remodeling accompanying DCM by stimulating apoptosis [52], but also by increasing AGEs formation and the number of AGE-receptors, thus triggering the activation of profibrogenic factors [21]. Excessive oxidants may also activate PKC, therefore contributing to insulin resistance [53].

Impaired calcium homeostasis

Because the main feature of DCM is a contractile dysfunction, it seemed obvious to look for potential defects in ion homeostasis, and especially Ca^{2+} homeostasis [54]. In db/db mice, Ca^{2+} cycling is fully disturbed due to reduced Ca^{2+} influx via L-type Ca^{2+} channels, lowered Ca^{2+} release from sarcoplasmic reticulum, slowed Ca^{2+} reuptake, and increased Ca^{2+} efflux [55]. In STZ-induced diabetic rats, the main cause for impaired Ca^{2+} cycling consists of depressed sarcoplasmic reticulum function through decreased expression of SERCA2a and the ryanodine receptor, whereas the L-type Ca^{2+} current is not significantly modified [56; 57]. In contribution to impaired Ca^{2+} cycling, diabetes mellitus is also accompanied by a marked switch of MHC expression from the alpha to the beta isoform. The V3 isozymes formed with βMHC have a lower Ca^{2+}-activated ATPase activity, which could mediate in part the diminished contractility of the diabetic heart [58]. Again, the switch in MHC isoforms and the decrease in SERCA2a expression in the diabetic state are rapid events which precede the venue of contractile function [38]. In humans, the heart of nonischemic heart failure patients shows a most important decrease in the expression of the myocyte enhancer factor 2C (MEF2C) and its regulated transcripts SERCA2a and αMHC when associated to diabetes mellitus [59].

As it could be expected, impaired Ca^{2+} homeostasis may be of major importance in the pathogenesis of DCM. It is of note that SERCA2a overexpression protected the heart of STZ-diabetic mice from severe contractile dysfunction [60]. Although this remains to be determined for DCM, cytoplasmic Ca^{2+} overload may participate to cardiac remodeling through a mitochondrial-dependent necrotic process [61]. Results suggest that impaired excitation/contraction coupling which results from inadequate Ca^{2+} homeostasis, rather than interstitial fibrosis, is linked to the early stages of diabetic diastolic dysfunction [62]. Interestingly, calcium transients are impaired in cardiomyocytes of normal mice treated with palmitate, whereas the same treatment improved the calcium transients in cardiomyocytes

isolated from db/db mice [63]. The discrepancy in results is explained by an absence of depolarization of the mitochondrial membrane potential and no increase in mitochondrial ROS production for the ob/ob cardiomyocytes [63]. Besides establishing new evidences for a tight link between metabolism, mitochondrial function, and cardiac contractility, this study further strengthens the notion that DCM may originate from an improper adaptation of the heart to a modified metabolic environment.

Conclusions

Most of our present knowledge on the pathogenesis of DCM is actually based on scattered data obtained from a wide variety of animal models. Even though a few of the proposed mechanisms have been presently investigated in humans, a particular attention should be paid to the dramatic changes in nutrient supply to the heart and the impaired cardiac metabolic flexibility. The mitochondrion appears to play a central role in the regulation of the mechanisms proposed to be involved in the development of DCM. While the features of lipotoxic cardiomyopathy have received much attention, both glucose and fatty acid derivatives may co-jointly determine the fate of cardiac remodeling and contractility in diabetes mellitus. Strategies aiming to restore normal heart metabolism in DCM should be expected to restore normal cardiac function. Glucolipotoxicity as a concept requires further investigation.

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Table

Proposed mechanisms in the pathogenesis of diabetic cardiomyopathy according to animal studies.

Mechanism	Pathology	Animal Model
Cell apoptosis and cardiac remodeling		
Overactivity of the renin-angiotensin system	T1DM	STZ-treated SD rats [20]
AGE and AGE receptors activation	T1DM	STZ-treated Wistar rats [21]
Intramyocardial inflammation	T1DM	STZ-treated SD rats [22; 23]
Switch in contractile protein expression	T1DM	STZ-treated Wistar rats [38; 58]
Metabolic derangements		
Increased fatty acid uptake	Lipotoxic CM	HFD-fed Wistar rats [33], CD36 deficiency in mice with cardiac PPARα overexpression [34]
Hyperglycemia-related alterations	T1DM, T2DM	Zucker diabetic fatty rats [36], STZ-treated FVB and db/db mice [37]
Impaired mitochondrial function		
Impaired ATP production	T1DM, T2DM	STZ-treated SD rats [43], db/db mice [48]
Alterations in cardiolipin content and composition	T1DM, T2DM	STZ-treated C57BL/6 and ob/ob mice [45]
Activation of the intrinsic pathway of apoptosis	T2DM	Zucker diabetic fatty rats [44]
Increased oxidative stress	T1DM, T2DM	OVE26 mice [49], ob/ob mice [51; 52], db/db mice [52], STZ-treated Wistar rats [21]
Impaired Ca^{2+} homeostasis	T1DM, T2DM	db/db mice [55; 63], STZ-treated Wistar rats [56; 57]

A brief overview of the results obtained from recent animal studies which are discussed further in the text. AGEs, advanced glycation end products; CM, cardiomyopathy; HFD, high fat diet; SD, Sprague Dawley; STZ, streptozotocin; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.