Diabetic cardiomyopathy: understanding the molecular and cellular basis to progress in diagnosis and treatment

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Abstract Diabetes mellitus is an important and prevalent risk factor for congestive heart failure. Diabetic cardiomyopathy has been defined as ventricular dysfunction that occurs in diabetic patients independent of a recognized cause such as coronary artery disease or hypertension. The disease course consists of a hidden subclinical period, during which cellular structural insults and abnormalities lead initially to diastolic dysfunction, later to systolic dysfunction, and eventually to heart failure. Left ventricular hypertrophy, metabolic abnormalities, extracellular matrix changes, small vessel disease, cardiac autonomic neuropathy, insulin resistance, oxidative stress, and apoptosis are the most important contributors to diabetic cardiomyopathy onset and progression. Hyperglycemia is a major etiological factor in the development of diabetic cardiomyopathy. It increases the levels of free fatty acids and growth factors and causes abnormalities in substrate supply and utilization, calcium homeostasis, and lipid metabolism. Furthermore, it promotes excessive production and release of reactive oxygen species, which induces oxidative stress leading to abnormal gene expression, faulty signal transduction, and cardiomyocytes apoptosis. Stimulation of connective tissue growth factor, fibrosis, and the formation of advanced glycation end-products increase the stiffness of the diabetic hearts. Despite all the current information on diabetic cardiomyopathy, translational research is still scarce due to limited human myocardial tissue and most of our knowledge is extrapolated from animals. This paper aims to elucidate some of the molecular and cellular pathophysiologic mechanisms, structural changes, and therapeutic strategies that may help struggle against diabetic cardiomyopathy.

Keywords Diabetic cardiomyopathy pathophysiology · Diastolic function · Hyperglycemia · Oxidative stress · Systolic function · Treatment

Introduction and definition of diabetic cardiomyopathy

Diabetes increases the risk of heart failure (HF) independently of other comorbidities. Diabetic cardiomyopathy has been defined as ventricular dysfunction that occurs in diabetic patients independent of a recognized cause, such as coronary artery disease (CAD) or hypertension [27, 234]. The term "diabetic cardiomyopathy" was initially introduced by Rubler in 1972 based upon postmortem finding on four diabetic adults who had HF in the absence of other comorbid conditions [171]. Later, this evidence was confirmed in large epidemiologic studies [102]. The term now includes diabetic individuals with diastolic dysfunction, with a prevalence as high as 60% in well-controlled type 2 diabetic patients [19, 51, 52, 145, 175]. However, the concept as a clinical entity remains vague, despite more than 35 years of basic and clinical investigations.

Experimental studies in dogs, monkeys, rabbits, and rodents have shown that diabetes causes myocardial fibrosis and myocyte hypertrophy, defects in cellular Ca^{2+} transport [72], myocardial contractile proteins [78], a shift in metabolism substrate, and an increase in reactive oxygen species (ROS) and collagen formation [166]. All these abnormalities result in structural and functional disturbances in the myocardium.

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Human diabetic cardiomyopathy is characterized by diastolic dysfunction, which may precede the development of systolic dysfunction [19, 120]. The earlier signs of ventricular dysfunction consist of impaired relaxation and decreased compliance with a reduction in early diastolic filling and an increase in atrial filling to which cardiac hypertrophy and fibrosis are the initial contributors. Although these features are characteristic of diabetes, they are by no means specific of this condition as older age, female gender, obesity, and hypertension all can lead as well to their development. As diabetes is increasingly recognized as a disease of the vasculature, working synergistically with concomitant dyslipidaemia, hypertension, and obesity, it becomes difficult to differentiate between a pure diabetic etiology and other contributing cardiovascular risk factors.

Prevalence and prognosis

The prevalence of diabetes mellitus (DM) is growing rapidly, and its global prevalence is expected to reach 300 million by 2025. The rising number of diabetic patients is due to an increase in population, urbanization, life expectancy, prevalence of obesity, and physical inactivity.

Diabetes mellitus is highly prevalent and an important risk factor for congestive HF. Indeed, cardiovascular complications are the leading cause of diabetes-related morbidity and mortality [199]. In the near future, the cardiovascular complications will be able to account for over 75% of deaths among DM population [105].

The Framingham Study [69, 102, 172] was a landmark by firmly establishing the epidemiologic link between diabetes and HF [102]. The risk of HF in diabetic subjects was increased 2.4-fold in men and fivefold in women. This risk was independent of age, hypertension, obesity, CAD and hyperlipidaemia. Furthermore, diabetic patients have an increased likelihood of developing HF following myocardial infarction (MI), and once established, the outcome is worse than in non-diabetics [45]. Indeed, diabetes represents even a stronger predictor of mortality than CAD in cohorts with HF [22]. This suggests that diabetic hearts have less reserve due to ongoing cellular damage and are more vulnerable to decompensation and failure through future cardiac events.

Similar findings have been reported in a number of other studies [23, 24, 97, 143, 144], including United Kingdom Prospective Diabetes Study [190], Cardiovascular Health Study [81, 110], Hypergen [152], Strong Heart Study [20, 96, 120] and Euro Heart Failure Surveys. All observed that there is a consistent association between diabetic cardiomyopathy and the presence of cardiac hypertrophy and myocardial stiffness, independently from other

comorbidities. Such associations have provided credible evidence to support the existence of diabetic cardiomyopathy as a unique clinical entity and that the presence of diabetes may independently increase the risk of developing HF. As an example, in a report of 9,591 subjects with type 2 diabetes and matched controls, HF was more frequent at baseline in diabetics (11.8 vs. 4.5 percent) [143]. This relationship was demonstrated in a report from the Studies of Left Ventricular Dysfunction (SOLVD) that enrolled 6,791 patients, including 1,310 with diabetes [184]. Compared with non-diabetics, diabetic patients were significantly more likely to be admitted for HF and had higher rates at 1 year of all-cause mortality (32 vs. 22 percent), cardiovascular mortality (28 vs. 19 percent), and mortality related to pump failure (11 vs. 6 percent) [54]. In the presence of coronary disease, diabetes was independent from other risk factors for predicting worsening of HF and it was the third most important, after age and LVEF. Recently, the publication of three major studies, ACCORD (Action to Control Cardiovascular Risk in Diabetes), ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation) and VADT (Veterans Affairs Diabetes Trial), raised concerns about whether intensive glucose control leading to low A1C and possibly more episodes of hypoglycemia could have negative health effects in some patients.

Evidence for diabetic cardiomyopathy

Although diabetic patients are at increased risk of structural heart disease due to vascular complications, the concept of diabetic cardiomyopathy suggests a direct myocardial insult. The natural history consists of a hidden subclinical period, during which cellular structural insults and abnormalities lead initially to diastolic dysfunction, then to systolic dysfunction, and eventually later to HF [15, 71, 189, 210]. Early along disease progression, left ventricular hypertrophy (LVH), and other structural changes act synergistically with the vascular consequences of hypertension and cardiac ischemia to precipitate overt clinical deterioration and ventricular failure.

Diastolic dysfunction in diabetes

Increased LV diastolic stiffness and relaxation disturbances are recognized as the earliest manifestation of DM-induced LV dysfunction. In fact, abnormal diastolic function has been noted in 27–70% of asymptomatic diabetic patients [151, 233], which may be in part due to increased LV mass and fibrosis [69]. Conversely, up to 37% of individuals with diastolic HF have diabetes [108], and when diabetes is

superimposed on diastolic HF, a significant reduction in 5-year survival is observed even after adjusting for covariates [203].

Changes in diastolic function are a widely reported finding in diabetic animals [73, 181] and humans without evidences of heart disease caused by other factors [6, 79, 118, 129, 153, 162, 163, 165, 183, 233]. In experimental diabetes, ventricular papillary muscles have showed the prolongation of relaxation and considerable slowing in relaxation velocity [30, 61, 204]. Additionally, isolated perfused hearts from type 2 diabetic rats showed prolonged isovolumic relaxation, increased late mitral inflow velocity, and augmented LV end-diastolic pressure [99]. In Otsuka Long-Evans Tokushima fatty (OLETF) rats, prolonged deceleration time and reduced peak velocity of early filling were shown [135], representing an early manifestation of abnormal LV diastolic function. Similarly, STZ-diabetic rats showed significant differences in early to late diastolic mitral inflow velocity ratio and isovolumic relaxation time, but not in fractional shortening, deceleration time, and myocardial collagen content. These findings suggest that the presence of diastolic dysfunction in diabetic hearts may relate to uncoupling of the contractile apparatus (which drives early relaxation), without concomitant increases in chamber stiffness (which produces later diastolic changes) [48].

Diastolic dysfunction parameters in diabetic patients are analogous to those in animal studies. Doppler echocardiography demonstrates either impaired relaxation or a pseudonormal filling pattern [71, 231]. Diastolic dysfunction is more abnormal in hypertensive patients and in those with worse glycemic control [120]. In fact, improvement in glycemic control has been demonstrated to improve cardiac function, suggesting that diabetic cardiomyopathy might be reversible in its early stages [36, 160, 195, 212, 213], although this subject has recently been questioned by several clinical trials [77, 154, 56].

Studies that have examined systolic and diastolic dysfunction in both type 1 and type 2 diabetes suggest that the latter is more susceptible to preclinical changes. Ventricular filling was significantly more impaired in the type 2 than in the type 1 diabetic patients, especially the peak early filling velocity E [16]. The mechanism of protection of type 1 diabetic patients may relate to the protective effects of insulin therapy and lack of insulin resistance. Indeed, animal data suggest the correction of abnormal function with insulin therapy, with parameters of cardiac performance significantly improved in insulin-treated rats when compared with non-treated animals [174].

Biopsies from diabetic patients showed that hypertrophy of myocardial cells and interstitial fibrosis of the myocardium are observed in mild stage of the disease [147]. However, a recent study has shown that mechanisms responsible for the increased diastolic stiffness of the diabetic heart are different in systolic and diastolic HF: in diabetic patients with systolic HF, fibrosis and deposition of advanced glycation end-products (AGEs) are the most important contributors to high LV diastolic stiffness, whereas in diabetic patients with diastolic HF, elevated resting tension of hypertrophied cardiomyocytes is the most important contributor to high LV diastolic stiffness [209].

Systolic dysfunction in diabetes

The major feature of systolic dysfunction is depressed LVEF. However, studies have shown that subtle systolic LV impairment may be missed on standard two-dimensional echocardiography, as the focus visually is on radial contraction and therefore early longitudinal dysfunction may be ignored [158]. In HF, reduced long axis shortening is seen and compensated by increased radial shortening.

Animal studies have shown diabetes to be also associated with systolic dysfunction [93, 99, 220]. In diabetic animals, heart rate, systolic blood pressure, and fractional shortening were significantly reduced in vivo compared with control animals [89]. In murine isolated papillary muscle preparations, active force was reduced by 61% [204]. These changes take some time to develop; systolic function was unchanged in 6-week-old db/db mice, but fractional shortening and velocity of circumferential fiber shortening were reduced in 12-week-old db/db mice relative to db/+control mice [181]. These studies suggest that duration of diabetes is crucial for systolic dysfunction.

These experimental findings are supported by both epidemiological and clinical studies. Friedman et al. [67] demonstrated that diabetic patients had an increase in end-systolic diameter and volume, a diminished left ventricular ejection fraction (LVEF), and a decreased minor axis shortening and velocity of circumferential fiber shortening. In a similar study of 40 type 2 normotensive diabetic patients, 55% patients had systolic dysfunction, but only 7.5% had electrocardiographic changes compatible with cardiac ischemia; 40% patients were also found to have LV hypertrophy [130]. Diabetic patients present a lower LVEF in response to exercise, suggesting a reduction in cardiac reserve [132, 139]. Furthermore, non-invasive evaluation of cardiac performance in these patients demonstrated a prolonged preejection period and a shortened ejection time, both of which correlate with reduced resting LVEF and diminished systolic function [234]. In a report from the Strong Heart Study, diabetic patients had higher LV mass, wall thickness, and arterial stiffness and reduced systolic function. These abnormalities were independent of body mass index and blood pressure [49].

Many studies have shown that diabetic patients have abnormal diastolic dysfunction but preserved systolic

function. However, Fang et al. suggested that this relates to the techniques used for systolic function evaluation, which, in the view of the author, are less sensitive than those used for the assessment of diastolic dysfunction. This author demonstrated that more sensitive techniques for systolic assessment such as strain, strain rate, and myocardial tissue Doppler velocity can detect preclinical systolic abnormalities in diabetic patients [62].

Nevertheless, the prognosis in patients with established systolic dysfunction is poor, and deterioration is further accelerated by concomitant diabetes. Therefore, attention has focused on establishing the importance of HF with preserved LV systolic function (diastolic HF) and determining criteria for diagnosing diastolic LV dysfunction, as these changes may precede systolic dysfunction and the onset of clinical symptoms.

Pathophysiologic mechanisms of diabetic cardiomyopathy

The pathogenesis of diabetic cardiomyopathy is multifactorial (Fig. 1). Several hypotheses have been proposed, including autonomic dysfunction, metabolic derangements, abnormalities in Ca^{2+} homeostasis, alteration in structural

proteins, and interstitial fibrosis. The variety of proposed mechanisms advanced for the pathogenesis of diabetic cardiomyopathy likely reflects the complex nature of this disease. The metabolic environment, characterized by hyperglycemia, hyperinsulinemia, and hyperlipidaemia, in which the diabetic heart functions, certainly triggers a substantial amount of cellular, structural, and functional alterations patent in the diabetic myocardial phenotype.

Hyperglycemia

Hyperglycemia represents one of the most important triggers of metabolic changes in diabetes. Hyperglycemic patients demonstrate an 8% increase in the risk of developing heart failure with every 1% elevation of glycosylated hemoglobin (HbAC1) [97]. This evidence was supported by another investigation involving 31,546 patients at high cardiovascular risk from two clinical trials [90]. In this study, each 18 mg/dL increase in baseline fasting plasma glucose was associated with a modest, but statistically significant, increase in the risk of HF hospitalization, at a mean follow-up of 2.4 years [23]. Cerutti et al. [37] reported a significant delay in LV filling in diabetic patients, proportional to the duration of diabetes. Other studies in type 1 diabetics have also demonstrated similar
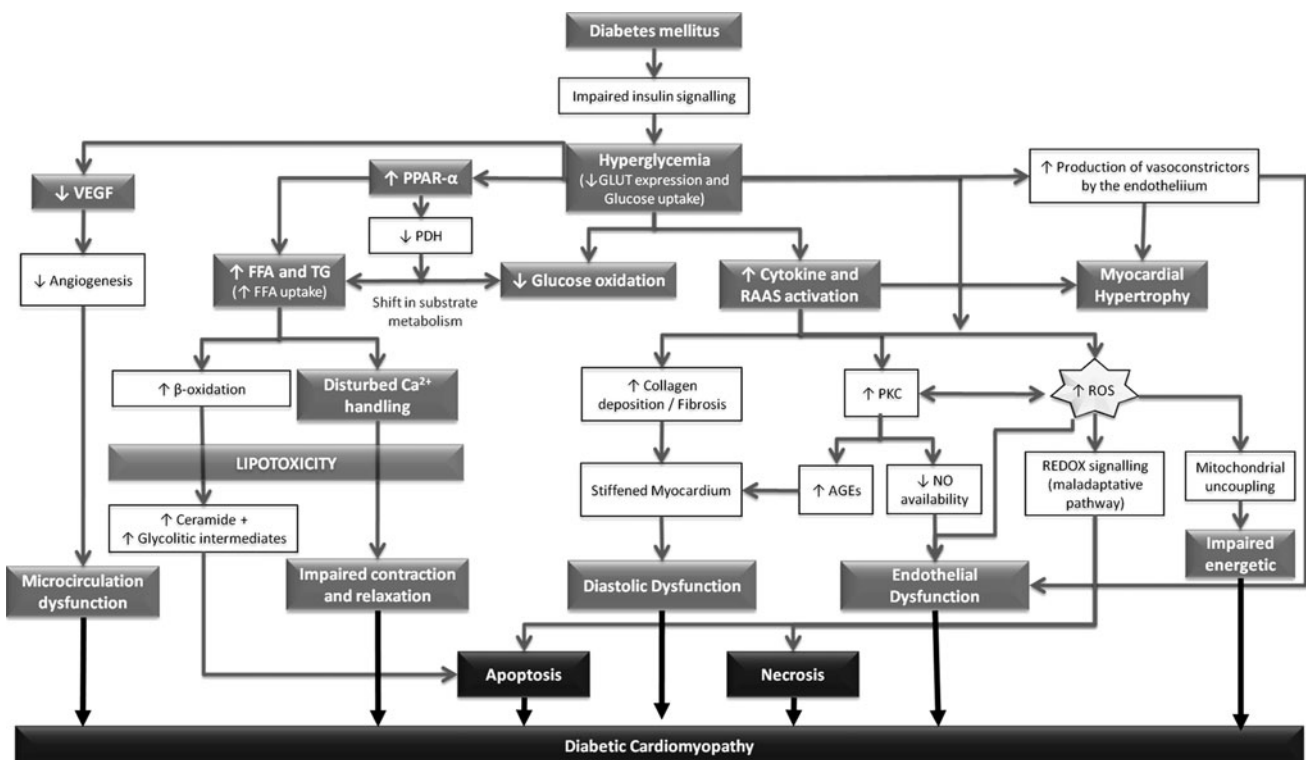

Fig. 1 Pathophysiologic mechanisms of diabetic cardiomyopathy. *AGEs* advanced glycation end-products, *FFA* free fatty acids, *GLUT* glucose transporter, *NO* nitric oxide, *PDH* pyruvate dehydrogenase, *PKC* protein kinase C, *PPAR-α* peroxisome proliferator–activated receptor-α, *ROS* reactive oxygen species, *TG* triglycerides, *VEGF* vascular endothelial growth factor

results [36, 98]. In type 2 diabetes, there is a close relationship between glycemic control and serum insulin-growth factor-I (IGF-I) level, with worse control being associated with lower IGF-I levels [75]. IGF-I has been shown to suppress myocardial apoptosis and improve myocardial function in various models of experimental cardiomyopathy. In a study of both type 1 and type 2 diabetic patients without overt systolic dysfunction and known heart disease, diastolic function was clearly impaired in both groups of patients, with ventricular filling being significantly more impaired in type 2 diabetic patients. There was a significant inverse correlation between glycosylated hemoglobin (HbA1C) and peak late filling velocity (A) in both groups of patients, and there was a direct correlation between diastolic velocity time integral and age, duration of diabetes, and HbA1C [16].

Pogatsa et al. [159] found that untreated hyperglycemic diabetic dogs had higher LV passive elastic modulus, increased LV end-diastolic pressures, and lower cardiac output than animals under chronic euglycemic therapy. There was also a close inverse relationship between cardiac output and passive elastic modulus [159]. An equivalent study in rats showed that diabetes caused significant decreases in resting LV systolic pressure, developed pressure, maximal velocity of tension rise (dP/dt_{max}), and the overall chamber stiffness constant, despite an increase in "operating chamber stiffness". Later in the progression of the disease, LV end-diastolic pressure, LV cavity/wall volume, end-diastolic volume, and time constant of LV relaxation were increased. All these abnormalities were reversed by insulin treatment [119]. In addition, the start point of insulin therapy seems to be important: early insulin treatment shortly reversed the marked structural changes associated with diabetes, such as increase in myocyte cross-sectional area and fibrosis, decrease in myofibrils and mitochondria volume or even capillary density and wall thickness, but were only selectively reversed by delayed insulin treatment once the extracellular matrix (ECM) alterations remained [201]. However, these experimental findings were questioned by recent randomized clinical studies [56, 77, 154].

Insulin resistance

Insulin resistance is an important risk factor for the development of cardiovascular diseases. On the other hand, HF causes insulin resistance and is associated with increased risk for the development of type 2 diabetes [8, 194]. As with the development of cardiovascular disease due to impaired insulin signaling, the development of insulin resistance in the heart failure patient is likely multifactorial. Possible mechanisms by which heart failure causes insulin resistance include sympathetic overactivity,

loss of skeletal muscle mass, sedentary lifestyle of the patient, and a potential effect of increased circulating cytokines, such as tumor necrosis factor-α (TNF-α), on peripheral insulin sensitivity [42, 112, 133]. A vicious cycle is therefore set in motion, in which HF and insulin resistance worsen one another.

Insulin resistance has been linked to early LV diastolic abnormalities in hypertension, independently of the influence exerted by increased blood pressure levels, overweight, and LV hypertrophy [70, 84]. Reduced insulin sensitivity can be found even in well-controlled type 2 diabetes without other comorbidities [26]. A study in rats has demonstrated that insulin resistance altered cardiac contractile function at the myocyte level [92]. Cardiomyocyte abnormalities in sucrose-fed rats were demonstrated in an insulin-resistant stage that precedes type 2 diabetes. In these animals, metformin prevented the development of sucrose-induced insulin resistance and the consequent cardiomyocyte dysfunction [57].

The molecular targets of insulin action and pathways of insulin signaling have been recently reviewed [157]. Insulin receptor binding induces receptor autophosphorylation and initiates phosphorylation cascades involving various signaling molecules within the cell. Several lines of evidence suggest that the most important step in insulin signaling is the translocation of the insulin-sensitive transport protein GLUT4 from an intracellular compartment to the sarcolemma [43]. Studies using specific inhibitors have revealed that the action of 4 protein kinases (phosphoinositol 3-kinase [PI 3-K], Akt/protein kinase B [PKB], and the atypical protein kinase C [aPKC] isoforms zeta and λ) are required for insulin-dependent sarcolemmal GLUT4 translocation [106, 157, 235]. Although specific defects in the muscle insulin receptor, insulin receptor substrates, PI 3-K, PKB, or aPKC would seem logical candidates for the inherited nature of muscle insulin resistance, isolated defects in these individual elements in fact only account for sporadic cases of diabetes [47]. In spite of all this amount of information, the specific defect in insulin-stimulated GLUT4 translocation, which conveys muscle insulin resistance, remains obscure. Therefore, the identification of novel pathways of the insulin-signaling cascade [17], and how factors such as fatty acids interact with components involved in insulin-mediated glucose transport [176], will surely clarify the complex genetic–environment interactions involved in the development of insulin resistance.

Myocardial fibrosis

Myocardial fibrosis and collagen deposition are the primary structural changes observed in diabetic cardiomyopathy. Animal studies with OLETF diabetic rats have shown

that their low peak velocity of early diastolic transmitral inflow and prolonged deceleration time were associated with extracellular fibrosis and higher transforming growth factor-β_1 (TGF-β_1) receptor II expression in LV myocytes when compared with control rats [135]. These results indicate that LV fibrosis occurs in early stages of type 2 diabetes. Accordingly, other experimental studies have also demonstrated the normalization of the collagen alteration by endurance training, begun relatively early in the disease process [192]. This improvement may be related to improved diabetic control due to increased insulin sensitivity caused by exercise training. More recently, myocardial fibrosis has been quantified in diabetic patients using new techniques such as the assessment of ultrasonic backscatter, which is directly related to collagen content. In a study of 26 asymptomatic type 1 diabetics without hypertension or CAD, integrated backscatter in the septum and posterior wall was significantly higher in diabetics compared with controls, corresponding to diastolic dysfunction, although global systolic function was preserved [50].

Diabetes locally activates myocardial renin–angiotensin–aldosterone system (RAAS) and endothelin systems [31], contributing to myocyte necrosis and fibrosis [39, 68]. The distribution of fibrous tissue in the myocardium is interstitial, perivascular, or both, and pathologic examination reveals myocardial hypertrophy, interstitial fibrosis, capillary endothelial changes, and capillary basal laminae thickening [65]. Deposition of collagen type I and III predominates in the epicardial and perivascular regions, whereas type IV predominates in the endocardium [183]. Collagen interacts with glucose, forming Schiff bases, which subsequently reorganize into glycated collagen (Amadori products). The Amadori products then undergo further chemical modification to form AGEs. The AGEs are a stable form of cross-linked collagen and are thought to contribute to arterial and myocardial stiffness, endothelial dysfunction, and atherosclerotic plaque formation. Correlations between AGEs serum levels and isovolumetric relaxation time and LV diameter during diastole have been reported in human patients with type 1 diabetes [21]. In the cardiovascular system, AGEs also might perform cross-linking of collagen with circulating proteins (e.g, low-density lipoprotein) and result in impaired cellular nitric oxide (NO) signaling through advance glycation end-product receptor (RAGEs) interactions. AGEs also exacerbate intracellular oxidative stress, which can contribute to cell damage [236]. Therefore, altered myocardial passive properties and impaired LV function (both diastolic and systolic) observed in patients with diabetes can be the result of fibrosis and altered collagen structure, specifically because of AGEs' increased collagen cross-linking [14, 208].

Myocardial hypertrophy

Structural changes in diabetic cardiomyopathy are related to adverse remodeling, consisting of LVH, diastolic left ventricular dysfunction (with concomitant atrial dilatation), and systolic dysfunction. Left ventricular hypertrophy is a hallmark in the morphologic manifestation of diabetic cardiomyopathy, generally representing a more advanced stage of the disease. It represents a LV mass excess, which leads to a 'stiffened' ventricle and precedes systolic LV dysfunction. The presence of hypertrophy in diabetic cardiomyopathy might not be associated with demonstrable LV diastolic dysfunction by conventional echocardiography (and vice versa). The Framingham study confirmed that LVH is indicative of a poor prognosis, and the adjusted cardiovascular risk was approximately 1.5-fold higher for increments of 50 g/m^2 in LV mass, as assessed by echocardiography [113]. Moreover, LVH is now recognized as an independent indicator of diastolic dysfunction if the diagnosis is clinically suspected. An LV wall mass index >122 g/m^2 in women or >149 g/m^2 in men is sufficient for the diagnosis of diastolic HF according to a recent consensus document from the European Society of Cardiology [156].

Finally, regression of LVH has been demonstrated with some interventions targeting diabetic cardiomyopathy. However, unlike hypertensive cardiomyopathy, the clinical significance of hypertrophy and its regression in diabetic cardiomyopathy remains to be determined.

Alterations in the metabolic substrate

Metabolic changes in diabetes are directly triggered by hyperglycemia [38]. In the absence of diabetes, approximately equivalent proportions of energy required for cardiac contractility come from glucose metabolism and free fatty acids (FFA), whereas in diabetes, myocardial glucose use is significantly reduced, with a shift in energy production toward FFA β-oxidation [168]. The reduction in glucose use in the diabetic myocardium results from depleted glucose transporter proteins, glucose transporter-1 (GLUT-1) and GLUT-4. In addition, high circulating free fatty acids (FFA) inhibit pyruvate dehydrogenase (PDH), which impairs myocardial energy production and leads to the accumulation of glycolytic intermediates and ceramide, enhancing apoptosis [58, 117]. Also, peroxisome proliferator–activator receptor-α (PPAR-α)-enhanced activity in DM increases the expression of pyruvate dehydrogenase kinase 4 and other genes involved in the regulation of cellular FAA uptake and β-oxidation and also reduces glucose oxidation.

Furthermore, elevated FFA levels are believed to be one of the major contributing factors in the pathogenesis of

diabetes. FFA result from enhanced adipose tissue lipolysis and hydrolysis of augmented myocardial triglyceride stores. They enhance peripheral insulin resistance and trigger cell death. Moreover, in addition to the FFA-induced inhibition of glucose oxidation, high circulating and cellular FFA levels may result in intracellular accumulation of potentially toxic intermediates of FFA (lipotoxicity), besides the abnormally high oxygen requirements during FFA metabolism. All these lead to morphological changes [140, 169, 223] and impaired myocardial performance [3, 125, 197]. Since the ischemic myocardium depends upon anaerobic metabolism of glucose, increased glucose uptake and metabolism are necessary for the maintenance of myocardial function [193, 219]. These changes increase myocardial oxygen utilization and can reduce the compensatory capacity of postinfarcted diabetic myocardium [168]. Although some controversy exists on whether diabetic hearts are more susceptible to injury when analyzed ex vivo [1, 127, 150, 216], most in vivo studies have supported a greater degree of reduction in LV function and accelerated LV remodeling in the hearts of diabetic animals after coronary artery ligation [82, 95, 155, 186, 200]. Several studies in the models of type 2 DM and insulin resistance suggest that insulin resistance per se might contribute to reduced myocardial recovery after ischemia [82, 95]. All these evidences support the idea that, after ischemic injury, the diabetic environment and associated myocardial changes sensitize the diabetic heart to dysfunction.

Oxidative stress

Reactive oxygen species include a range of highly reactive oxygen–based molecules that consist of both free radicals and chemicals capable of generating free radicals. Although in health the primary source of ROS is the mitochondria, they are also produced by a range of other sources as a consequence of various disease states. Oxidative stress exists when the production of ROS outweighs their degradation by antioxidant defenses. The resultant elevation of ROS has numerous harmful effects on the cardiovascular system via cellular damage by oxidation, disruption of vascular homeostasis through interference with NO, and most recently discovered, by the modulation of detrimental intracellular signaling pathways, the so-called redox signaling [205]. In a variety of animal models of diabetes [221] and humans with diabetic cardiomyopathy, there is excessive ROS production from both mitochondrial and extra-mitochondrial sources, and ROS has been implicated in all stages of the development of HF, from cardiac hypertrophy to fibrosis, contractile dysfunction, and failure [180]. The increase in ROS causes cardiac dysfunction by direct damage to proteins and DNA, as well as by promoting

apoptosis. Furthermore, over-expression [116] or pharmacological administration [33] of the antioxidant metallothionein in the rodent models of diabetes has been shown to ameliorate the morphological and functional characteristics of diabetic cardiomyopathy. Similar results have been reproduced using other antioxidants in the rodent models of both type 1 and type 2 diabetes [224].

Recently, nicotinamide adenine dinucleotide phosphate (NADPH) oxidase enzymes have received growing attention as a source of ROS and particularly for their involvement in redox signaling [180]. These enzymes act as catalysts for electron transfer from NADPH to molecular oxygen, resulting in the generation of free radicals. Through interaction with a variety of transcription factors, redox signaling influences the expression of growth-related genes and in turn affects contractile function [74]. NADPH oxidase is increased in both failing [115] and diabetic [221] rodent hearts. In diabetic rodents, the up-regulation of NADPH oxidase correlates with morphological evidence of cardiac hypertrophy and up-regulation of pro-fibrotic genes such as pro-collagen III, which can be ameliorated using the antioxidant Tempol [167]. ROS also react directly with NO to form peroxynitrite species, thereby inactivating the vasodilatory effect of NO, which is essential to vascular homeostasis and endothelial function. Antioxidants such as vitamin C are capable of restoring endothelial function in patients with HF [94]. Reductions in the release of NO from endothelial cells, as a consequence of ROS, have also been shown to affect ventricular relaxation in LVH [124].

Myocyte cell death

Myocyte cell death may be caused by apoptosis, necrosis, or both. The diabetic myocardium is susceptible to higher rates of myocyte death by both apoptosis and necrosis than that of healthy hearts. In a study of diabetic and diabetic-hypertensive hearts, myocyte necrosis was 1.4-fold more prevalent in patients with diabetes and hypertension than with diabetes alone, whereas myocyte apoptosis was not affected by the addition of hypertension [68]. These two distinct forms of cell death also have different consequences. Apoptosis does not cause scar formation or significant interstitial collagen accumulation [88], with nuclear fragmentation and cell shrinkage being replaced by the surrounding cells [10, 76]. Conversely, myocyte necrosis results in the widening of the extracellular compartments between myocytes and increased deposition of collagen in a diffuse or scattered manner [11, 114], resulting from both replacement fibrosis due to myocyte necrosis and connective tissue cell proliferation [218].

The hyperglycemia-induced ROS production contributes to accelerated apoptosis. Some of this proapoptotic effect of hyperglycemia is triggered by glycosylation and

phosphorylation of p53 and excessive synthesis of angiotensin II [63]. However, whether increased apoptosis itself is a cause or consequence of diabetic cardiomyopathy remains to be determined.

Contractile dysfunction and Ca^{2+} handling abnormalities

Abnormal Ca^{2+} handling in the cardiomyocyte is perhaps the mechanistic hallmark of diabetic cardiomyopathy: calcium is one of the principal ionic regulators in the heart and is essential for the process of excitation–contraction coupling and therefore primary to normal cardiac function (Fig. 2). In rodent models of both type 1 and type 2 diabetes, there is a wealth of evidence demonstrating altered expression, activity, and function of all transporters involved in excitation–contraction coupling: sarcoplasmic reticulum Ca^{2+}-ATPase (SERCA-2a) [204], Na^+/Ca^{2+} exchanger (NCX), ryanodine receptor (RyR) [87], plasma membrane Ca^{2+}-ATPase (PMCA) [80], as well as dysfunctional intracellular calcium signaling [211] (Fig. 2).

Among these alterations, those affecting the activity of SERCA-2a and of its inhibitor phospholamban (PLB) appear particularly pertinent to the pathogenesis of diabetes-induced cardiac dysfunction. PLB protein and mRNA levels were significantly increased in diabetic rats [104]. Depressed SERCA-2a activity will cause inefficient sequestration of Ca^{2+} in the sarcoplasmatic reticulum (SR), resulting in Ca^{2+} overload in the cytosol and impaired relaxation, which would correlate with clinical findings of diastolic dysfunction [187]. Indeed, over-expression of SERCA-2a improves calcium handling [211] and protects against cardiomyopathy in diabetic rodents [204]. Additional consequences of these changes include alterations to the Ca^{2+} sensitivity of regulatory proteins involved in the regulation of the cardiac actomyosin system, such as phosphorylation of sarcomeric protein troponin I [125] and shifts in cardiac myosin heavy chain isoforms (V1 → V3) [197]. Even if Ca^{2+}-handling studies in human hearts are challenging, further investigation is required to characterize these mechanisms in patients with diabetic cardiomyopathy.
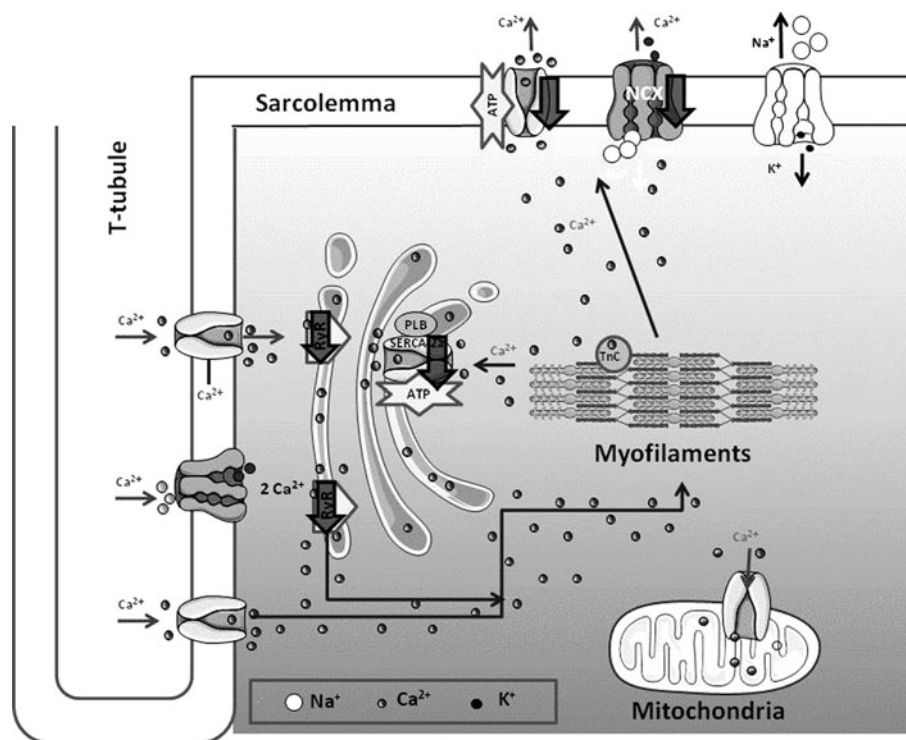

Fig. 2 Ca^{2+} handling in ventricular myocytes. In the cardiomyocyte, Ca^{2+} influx induced by the activation of voltage-dependent L-type Ca^{2+} channels on membrane depolarization triggers the release of Ca^{2+} via Ca^{2+}-release channels (ryanodine receptors, RyR) of sarcoplasmic reticulum (SR) through a Ca^{2+}-induced Ca^{2+}-release mechanism. Ca^{2+} then diffuses through the cytosolic space to reach contractile proteins, binding to troponin C and resulting in the release of the inhibition induced by troponin I. By binding to troponin C, the Ca^{2+} triggers the sliding of thin and thick filaments, which results in cardiac force development and/or contraction. $[Ca^{2+}]$ and then returns to diastolic levels mainly by the activation of the SR Ca^{2+} pump (SERCA2a), the sarcolemmal Na^+/Ca^{2+} exchanger, and the sarcolemmal Ca^{2+}-ATPase. The *black arrow* indicates the down-regulation of specific transporters/exchangers in diabetic cardiomyopathy. Figure was produced using Servier Medical Art

Increased activity of PARP enzyme

Poly-(ADP-ribose) polymerase (PARP) is a nuclear DNA repair enzyme with multiple regulatory functions. PARPs are over-activated in diabetes [222] as a reparative response to increased oxidative and nitrosative stress and their subsequent damage to DNA. PARP activation, on the one hand, depletes its substrate, NAD^+, slowing the rate of glycolysis, electron transport, and ATP formation. Furthermore, it inhibits GAPDH by poly(ADP-ribosy)lation leading to the accumulation of glycolytic intermediates that in turn activate a series of transducers which inflict further damage via AGE formation and protein kinase C (PKC) activation [55]. These processes result in acute endothelial dysfunction in diabetic blood vessels, which importantly contributes to the development of various diabetic complications [150]. PARP also promotes cardiac damage by activating nuclear factor κB (NFκB) [196] and inducing over-expression of the vasoconstrictor endothelin 1 (ET-1) and its receptors [134].

Increased activity of protein kinase C

There is increased activity of PKC in both failing [28] and diabetic [217] hearts, and levels correlate with both ROS [107] and PARP [55]. PKC phosphorylates a number of proteins directly involved in cardiac excitation–contraction coupling and therefore disturbs Ca^{2+} handling in cardiomyocytes [29]. Transgenic mice over-expressing the PKC-β_2 isoform in the myocardium develop cardiac hypertrophy, fibrosis, impairment of left ventricular performance, and progressive cardiomyopathy [215]. Inhibition of PKC-α [86] or PKC-β [215] is also associated with significant improvements in cardiac function in the rodent models of heart failure in conjunction with an improved myocardial metabolic gene profile, glucose utilization, and diastolic function as evidenced by MR spectroscopy [12].

Neurohumoral activation

Enhanced activity of local RAAS in diabetes induces functional abnormalities in ventricular myocytes [161]. Activation of the RAAS during DM is associated with increased NADPH oxidase activity through direct signaling pathways with angiotensin type-1 receptor (AT$_1$). Consequent ROS elevation causes oxidative damage to cardiomyocytes and results in endothelial cell apoptosis [68, 161]. The effects of angiotensin II may also be promoted by the production and release of TGF-β_1 by cardiac fibroblasts [34, 109]. TGF-β_1 plays a critical role in organ morphogenesis, development, growth regulation, cellular differentiation, gene expression, and tissue remodeling. TGF-β_1 induced by metabolic abnormalities (chronic postprandial hyperglycemia, hyperinsulinemia, and insulin resistance) has also been implicated in the development of diabetic cardiomyopathy. In the rat heart, TGF-β increases fibrous tissue formation and up-regulates collagen expression during tissue repair by binding to the TGF-β type 2 receptor.

Angiotensin II receptor blockers have been shown to attenuate metabolic and cellular changes in the hearts of diabetic rodents [164] and reduce the levels of ROS [64]. Blockade of angiotensin II is also capable of restoring SERCA-2a activity, thereby improving intracellular Ca^{2+} handling in heart failure [121]. As both angiotensin II and aldosterone induce cardiac fibrosis through enhanced accumulation of collagen and increased fibroblast proliferation [131], it has been suggested that aldosterone and glucose mediate cardiac fibrosis through the stimulation of myofibroblast growth in patients with a dysregulated RAAS, a pathway of cardiac pathology which is intensified by hyperglycemia [142]. This will ultimately contribute to cardiac fibrosis and hypertrophy, which manifests itself clinically by diastolic dysfunction.

Cardiac autonomic neuropathy

Cardiac autonomic neuropathy plays an important role in the development of left ventricular dysfunction [234] and is associated with increased cardiovascular risk in diabetic patients. Extensive evidence has demonstrated the association of autonomic dysfunction with impaired vasodilator response of coronary resistance vessels to increased sympathetic stimulation [53] and abnormal cardiac function in diabetes [59, 101, 165]. Sympathetic stimulation improves left ventricular contraction and increases LV relaxation rates, perhaps by facilitating calcium uptake by the SR.

Sympathetic denervation is an important feature of cardiac autonomic neuropathy in diabetes. Several authors have demonstrated cardiac sympathetic dysfunction in diabetic patients, even without myocardial perfusion abnormalities [126, 177]. At the same time, others have described a correlation between myocardial sympathetic innervation derived from scintigraphy analysis and the E/A ratio in Doppler echocardiography, providing evidence that an abnormal sympathetic innervation of the heart may contribute to a disturbance in LV filling [136, 138]. This effect was more severe in type 2 diabetes patients than that in type 1 patients, particularly involving inferoposterior segments of the heart [206].

Norepinephrine content and β-adrenergic receptor density are also significantly increased in short-term diabetics, enhancing cardiac sympathetic activity, which may induce toxic effects on the heart. Over-expression of β_1-adrenergic receptors causes marked myocyte hypertrophy, interstitial fibrosis, and reduced contractile function, accompanied by increased myocyte apoptosis [25, 225]. However, as the

diabetic state progresses, cardiac norepinephrine content, β-adrenergic receptor density, and adenylyl cyclase activity return to control levels [207]. Indeed, autopsy studies have found that myocardial catecholamine stores are depleted in long-term diabetic patients which could relate to systolic and diastolic dysfunction [141]. Moreover, these changes are probably associated with functional impairment in cardiac sympathetic nerve fibers [178].

Structural abnormalities of the vessels

The capacity of the vascular bed to meet metabolic demands may be impaired by abnormal epicardial vessel tone and microvascular dysfunction [71].

Hyperglycemia leads to an enhanced synthesis of vasoconstrictor prostanoids by the endothelium and activation of PKC. Protein kinase C, an intracellular signaling molecule, is activated in diabetes and can lead to endothelial dysfunction and impaired endothelium-dependent relaxation [100], defects that may be related to inactivation of NO by AGEs and increased generation of free radicals [32]. The abnormal vasodilator response in diabetes extends to the coronary microcirculation [179].

Over a chronic hyperglycemic period, a number of subsequent vascular changes develop. These changes comprise abnormal vascular sensitivity and reactivity to various ligands, depressed autonomic function, increased stiffness of the vascular wall and abnormalities of various proteins that control ion movements, particularly intracellular Ca^{2+} [146, 191].

Hypoxia-inducible factor-1 and vascular endothelial growth factor

An inadequate angiogenic response to ischemia in the myocardium of diabetic patients could result in poor collateral formation and hence an increased propensity to infarction with a reduced reparative response. Normally, vascular cells are activated by various stimuli, particularly hypoxia, as occurs in ischemia/infarction. The hypoxic stimulus is mediated chiefly through hypoxia-inducible factor 1 (HIF-1), a transcriptional regulator complex that controls the expression of multiple angiogenic growth factors, of which VEGF has received particular attention [122].

VEGF has been shown to contribute to the development of collateral vessels [2] and is expressed in increased quantities in cardiac myocytes and arteriolar smooth muscle cells following myocardial infarction (MI) in non-diabetic patients [185]. HIF-1α mRNA is up-regulated in patients with acute ischemia or early infarction, whereas VEGF transcripts are seen at a later stage in patients with evidence of developing infarction [111]. In contrast, in diabetes, the expression of mRNA and protein for VEGF and its receptors, VEGF-R1 and VEGF-R2, has been shown to be significantly decreased (40–70%) in the myocardium of both diabetic and insulin-resistant non-diabetic rats, together with a twofold reduction in VEGF and VEGF-R2 in ventricles from diabetic patients compared with non-diabetic donors [41]. This suggests that, in diabetic patients, the normal molecular processes that regulate angiogenesis may be impaired, although to date there are no direct studies to substantiate this.

Moreover, microcirculatory dysfunction in diabetics may be due in part to down-regulation of the expression of vascular endothelial growth factor (VEGF). In an animal model, local replacement of VEGF via DNA gene therapy was associated with increased capillary density and a significant improvement in cardiac function [226].

Therapeutic management of diabetic cardiomyopathy

Diabetic cardiomyopathy appears to consist of two major components, the first being a short-term, physiological adaptation to metabolic alterations, whereas the second represents degenerative changes whereby the myocardium displays limited capacity for repair. Nevertheless, there is a serious paucity of trial data in patients with diabetic cardiomyopathy and its earlier diastolic dysfunction stage and, as a consequence, no specific therapies are currently recommended. It is clear that once diabetic cardiomyopathy is established, the prognosis is very poor and management extremely challenging. For these reasons, therapies during the early stages of diabetes can potentially delay or impede the progression of more permanent damages. However, it should be noted that many factors such as the type of treatment, metabolic characteristics, lipid profile, and other individual differences may affect the process of development of diabetic cardiomyopathy, and not all diabetic patients are affected by the same factors or to the same degree, which may result in marked variability in the clinical manifestations of diabetic cardiomyopathy. Attention has therefore to be focused on a holistic approach in preventing causative insults, including hyperglycemia, insulin resistance and increased fatty acids, as well as lifestyle interventions.

Hyperglycemia increases FFA levels, oxidative stress, and growth factors and causes abnormalities in substrate supply and utilization, calcium homeostasis, lipid metabolism, and microvasculature; so tight glycemic control seems a logic and attractive strategy for preventing the development of diabetic cardiomyopathy. Indeed, until recently, evidences suggested that good diabetic control was beneficial, at least in the early stages of myocardial dysfunction [212, 213]. However, although glycemic

control is epidemiologically associated with decreased cardiovascular events, many prospective randomized clinical trials, such as ACCORD, ADVANCE, and VADT, failed to conclusively demonstrate that aggressive glycemic control improves the cardiovascular prognosis of patients with type 2 DM, especially those with long-standing DM. Furthermore, some of the therapeutic drugs for type 2 DM, in addition to their glucose-lowering actions, have properties that may reduce or increase cardiac events.

The ACCORD analysis confirmed that low A1c levels did not cause the increased mortality rate seen among patients who received intensive glycemic control (targeting A1c <6%) compared with those in the standard-control group (A1c target, 7–9%) [77].

In ADVANCE study, intensive control reduced the incidence of combined major macrovascular and microvascular events (∼10%) primarily because of a reduction in the incidence of nephropathy (∼21%) with no significant effect on retinopathy. However, this trial showed that there were no significant effects of the type of glucose control on death from cardiovascular causes [154].

Later, VADT trial analysis revealed that type 2 diabetic patients who received intensive control of type 2 diabetes in the first 15 years after their diagnosis had lower risk of fatal or non-fatal heart attacks and stroke. On the contrary, when intensive control did not begin until 16–20 years after the diagnosis, there was no cardiovascular benefit. The new analysis of VADT showed that intensive therapy (targeting A1c <7%) with rosiglitazone did not increase deaths versus standard therapy (A1c 8–9%) among subjects with diabetes. While the study failed to meet its primary endpoint (time to occurrence of a major cardiovascular event), there was a trend toward reduction in all cardiovascular events, but not in cardiovascular death, among subjects who received intensive treatment [56].

Firm recommendations regarding the choice of current *glucose-lowering therapies* in patients with diabetic cardiomyopathy cannot be made because of a lack of evidence. However, glucagon-like peptide-1 analogs have demonstrated the ability to improve hemodynamic variables in diabetic patients without overt HF. Improved cardiac parameters also have been noted with this agent class in postinfarction and in populations with advanced HF [202].

Thiazolidinediones (*TZD*) are a new class of compounds for the treatment of patients with type 2 diabetes mellitus, which act by increasing insulin sensitivity in skeletal muscle and adipose tissue through binding and activation of peroxisome proliferator–activated receptor-δ (PPAR-δ), a nuclear receptor that has a regulatory role in the differentiation of cells. Additionally, they also act on PPAR-α and increase serum HDL (high-density lipoprotein) cholesterol, decrease serum triacylglycerols (triglycerides), and increase LDL cholesterol levels marginally (pioglitazone to a lesser extent) [66]. To generate sufficient energy to sustain cardiac contractility, myocardial metabolism utilizes a range of substrates including NEFAs (nonesterified fatty acids), glucose, and lactate. However, in type 2 diabetes, as a consequence of insulin resistance, glucose is under-uptaked and NEFA metabolism is increased, impairing contractility. TZDs, apart from insulin-sensitizing fat and skeletal muscle, increase the expression and function of glucose transporters in the heart, leading to improved glucose metabolism, and reduce NEFA utilization by the myocardium [227]. As a consequence, they protect against myocardial injury associated with ischemia and improve the recovery of function following ischemia.

There is strong evidence that TZDs contribute to fluid retention by inducing sodium reabsorption by renal collecting tubule cells [83], and increase the risk of HF [57, 60–65]. This incidence of heart failure was not limited to the elderly and occurred with both high and low doses after a median treatment carried along 24 weeks. As a result, TZDs are not recommended in patients with symptomatic HF and are contraindicated in New York Heart Association (NYHA) class III or IV HF. TZDs may be considered as part of diabetes management in selected patients with class I-II HF with careful monitoring for fluid retention. Current evidence does not support the preferential use of TZDs for the purpose of improving cardiovascular risk.

Metformin is contraindicated in diabetic HF patients requiring pharmacologic therapy because of the risk of lactic acidosis, especially in the presence of hemodynamic instability or of other concurrent medical conditions such as renal insufficiency, liver disease, or severe infection with decreased tissue perfusion. Nevertheless, metformin is an effective and useful agent in the management of DM, and the general safety and possible survival benefit from metformin in this setting have been suggested by observational studies [60, 128].

Intracellular retention of calcium in diabetes is associated with depletion of high-energy phosphate stores and a derangement of ultrastructure and cardiac dysfunction. *Calcium channel blockers* are capable of reversing the intracellular calcium defects and preventing diabetes-induced myocardial changes. Verapamil has been shown to significantly improve the depressed rate of contraction and rate of relaxation, lower peak LV systolic pressure, and elevated LV diastolic pressure [4], as well as to improve the altered myofibrillar ATPase activity, myosin ATPase, myosin isoenzyme distribution, and SERCA-2a in streptozocin-induced diabetic rats [5].

Conventionally, there has been a reluctance to use *β-blockers* in diabetic patients for apprehension of adverse effects on insulin resistance and an unawareness of hypoglycaemia. However, with the recent advances in the understanding of HF and the awareness of the importance of the sympathetic nervous system in the release of vasoactive substances, *β*-blockers have become an essential treatment for HF [123]. Indeed, in a meta-analysis of *β*-blocker trials in HF, the survival benefit with beta blocker therapy was significant for both diabetic and non-diabetic patients [182]. The difference in risk reduction between diabetics and non-diabetics was not significant. *β*-blockers have been shown to prevent and even reverse cardiac remodeling, resulting in improved LV function and a reduction in mortality [123]. To summarize, *β*-blockers should be given to all diabetic patients with any evidence of HF, unless specifically contraindicated. This will result in mortality risk reduction despite the lower prognostic benefit on diabetics when compared with non-diabetic patients.

The important role of the RAAS in the pathogenesis of complications in diabetic patients is well described. Evidence supports the use of *angiotensin-converting enzyme (ACE) inhibitors* in preventing coronary perivascular and interstitial fibrosis, cardiac hypertrophy, and myocardial mechanical dysfunction associated with diabetic cardiomyopathy [7, 170, 232]. ACE inhibitors can also improve insulin action at the cellular level [188, 214]. ACE inhibition independently increases the basal and insulin-stimulated rate of glucose uptake in skeletal muscle in insulin-resistant obese Zucker rats by improving postreceptor insulin signaling and enhancing GLUT-4 translocation to the cell membrane [91]. Significant benefits were obtained for both cardiovascular morbidity and mortality in the HOPE (Heart Outcomes Prevention Evaluation) study with ramipril in 9,297 high-risk patients [229], but this benefit was even more impressive in the diabetic patients [229]. Furthermore, HOPE demonstrated a 33% reduction in the rate of development of new HF [13] and a 44% reduction in the risk of developing type 2 diabetes [230]. Additionally, SOLVD and SAVE trials and meta-analysis showed that diabetics benefit from ACE inhibitors to the same degree as non-diabetics [137, 182, 184].

Also *angiotensin receptor blockers (ARB)* have demonstrated cardiovascular protection in diabetic patients. Such is the case of candesartan that improved echocardiographic parameters of diastolic dysfunction, decreased collagen synthesis, and increased collagen degradation in asymptomatic diabetic subjects [103]. The possible preventive effect of losartan (ARB) in diabetic patients with type 2 diabetes was evaluated in a subset analysis of two large randomized trials: RENAAL for renal protection and LIFE for hypertension with left ventricular hypertrophy

[35]. Compared to placebo, losartan significantly reduced the incidence of first hospitalization for HF: 39 versus 54 percent in RENAAL and 11 versus 19 percent in LIFE. These findings support the use of ACE inhibitors or ARBs for the treatment of hypertension and renal disease in patients with diabetes.

Evidence also suggests a beneficial effect of *aldosterone antagonism* in diastolic heart failure by virtue of their beneficial effects on cardiac hypertrophy and fibrosis [148, 198]. These findings underscore the critical importance of inhibiting the RAAS in diabetic patients, especially when diastolic dysfunction is present and the process is, at least, partially reversible.

It has been shown that hyperglycemia may lead to an increase in the basement membrane protein, fibronectin via an endothelin (ET)-dependent pathway involving the activation of NF-kappa B and activating protein-1 (AP-1). Chen et al. [40] showed that the myocardium of diabetic rats is associated with an increase in myocardial fibronectin mRNA and increased ET-1 mRNA expression. This increase in fibronectin is dependent on ET receptor-mediated signaling. Bosentan, an *ET-receptor antagonist*, prevents the formation of collagen IV and fibronectin in the heart of streptozotocin (STZ)-induced diabetic rats [40, 173].

Targeting reduction of ROS or increasing *antioxidant* activity would intuitively represent novel therapeutic modalities against diabetic cardiomyopathy. Clinical studies, however, have been unable to translate these promising scientific data to the bedside, and several large randomized trials were unable to report any benefits of antioxidants on cardiovascular outcome in high-risk individuals [228].

Last but not least, *exercise* may improve glucose homeostasis by reducing the glucose/insulin ratio and increasing insulin sensitivity. Studies have shown that exercise training increases whole body insulin sensitivity and glucose oxidation by skeletal and cardiac muscle. The improvement may be associated with an increase in myocardial sarcolemmal GLUT-4 protein in diabetic hearts [85, 149]. In addition, exercise training improves cardiac output [46] and reverses the changes in the contractile properties of the heart in STZ-diabetic rats [44]. However, whereas low-intensity exercise training seems to improve cardiovascular function, some types of endurance training may further decrease the reduced myocardial Ca^{2+}-activated ATPase and *β*-adrenergic receptor number in diabetes [18].

Conclusion

As HF mortality remains high in DM despite the proven efficacy of current treatments, a better understanding of the pathophysiology of high LV diastolic stiffness could be

beneficial for *novel therapeutic strategies*. These therapies should be directed toward the prevention of diabetic cardiomyopathy progression in the early stages of clinical development and target either enhanced fibrosis/collagen deposition or alterations in cardiomyocyte metabolism. The majority of the agents listed below are in experimental stages, and none of them have been approved for use in diabetic cardiomyopathy. Notable among these novel agents are advance glycation end-product inhibitors (e.g, aminoguanidine, alanine aminotransferase 946, and pyridoxamine); advance glycation end-product cross-link breakers (e.g, alanine aminotransferase 711); and copper chelation therapy (e.g, trientine). Modulators of free fatty acid metabolism, such as trimetazidine, have proven useful in the management of angina, but their efficacy on diabetic cardiomyopathy is unknown. Also, blocking PARP activity with two different competitive PARP inhibitors provides an attractive approach as it blocks the activation of all major pathways thought to mediate tissue damage in diabetes [55].

In conclusion, diabetic cardiomyopathy progression can be summarized in three stages:

1. It is initiated by hyperglycemia at an early stage and characterized by metabolic disturbances and endothelial dysfunction. At this stage, myocardial structure is nearly normal and only substructural changes in myocytes are observed.
2. At an intermediate stage, cellular changes result in myocyte injury, loss, myocardial fibrosis, and hypertrophy. These changes initially cause abnormal mitral inflows that may advance to low ejection fraction. Patients at this stage may have minor changes in structure and significant changes in diastolic and systolic function.
3. In the most advanced stage, diabetic hearts present further changes in metabolism and development of myocardial fibrosis which result in myocardial microvascular changes. At this stage, diabetic hearts present marked changes in cardiac structure and function and are frequently associated with hypertension and early development of ischemic heart disease.

There are two important components in the clinical diagnosis of diabetic cardiomyopathy: the detection of myocardial abnormalities and the exclusion of other contributory causes of cardiomyopathy. Even though currently there is still no consensus in the precise imaging definition of diabetic cardiomyopathy, evidence of hypertrophy or diastolic dysfunction is likely crucial to support a diagnosis of diabetic cardiomyopathy but is not specific to it. In an attempt to overcome this fact, Aneja has recently proposed an imaging definition of diabetic cardiomyopathy that includes features such as evidence of cardiac hypertrophy

determined by conventional echocardiography or cardiac magnetic resonance imaging and/or evidence of LV diastolic dysfunction (with or without LV systolic dysfunction), including transmitral Doppler or tissue Doppler imaging (TDI), evidence of left atrial enlargement, abnormalities detected by novel imaging techniques or provocative testing (e.g, strain and strain rate imaging or stress imaging) [9].

Multiple pathophysiologic mechanisms have been proposed to explain this entity, but hyperglycemia seems to be the central mechanism triggering the processes that lead to the ultimate pathologic changes of myocardial hypertrophy, fibrosis, and collagen deposition. From epidemiologic studies, the natural history of diabetic cardiomyopathy seems to start with impaired glucose tolerance and possibly takes years to reach overt LV systolic or diastolic dysfunction. The key issue is that diabetic individuals are undoubtedly at a significant risk of cardiac failure, regardless of whether this results from diabetes itself or from the combination of several cardiovascular risks. Therefore, cardiometabolic prevention, focusing on dyslipidaemia, hypertension, and dysglycaemia, should form the basis in the management of these high-risk individuals.

There is a lack of clinical intervention trials, specifically in patients with diabetic cardiomyopathy. For this reason, no evidence-based interventions for the specific treatment of diabetic cardiomyopathy can be currently recommended.

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