

# Diabetic cardiomyopathy: from the pathophysiology of the cardiac myocytes to current diagnosis and management strategies

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**Abstract:** Diabetic cardiomyopathy (DCM), although a distinct clinical entity, is also a part of the diabetic atherosclerosis process. It may be independent of the coexistence of ischemic heart disease, hypertension, or other macrovascular complications. Its pathological substrate is characterized by the presence of myocardial damage, reactive hypertrophy, and intermediary fibrosis, structural and functional changes of the small coronary vessels, disturbance of the management of the metabolic cardiovascular load, and cardiac autonomic neuropathy. These alterations make the diabetic heart susceptible to ischemia and less able to recover from an ischemic attack. Arterial hypertension frequently coexists with and exacerbates cardiac functioning, leading to the premature appearance of heart failure. Classical and newer echocardiographic methods are available for early diagnosis. Currently, there is no specific treatment for DCM; targeting its pathophysiological substrate by effective risk management protects the myocardium from further damage and has a recognized primary role in its prevention. Its pathophysiological substrate is also the objective for the new therapies and alternative remedies.

**Keywords:** cardiovascular disease, atherosclerosis, cardiac autonomic neuropathy, echocardiography, treatment strategies

## Introduction

Cardiovascular disease is a common complication of diabetes responsible for 80% of the mortality in the diabetic population.<sup>1</sup> Coronary artery disease is the leading cause for the increased cardiovascular morbidity and mortality in diabetes, and atherosclerosis of the coronary vessels is its initial pathogenetic mechanism. Coronary artery disease and hypertension can account for most of the myocardial abnormalities (left ventricular [LV] hypertrophy and impaired contractility) that occur in diabetes. However, postmortem, experimental, and observational studies also provide evidence for a specific cardiomyopathy in diabetes, which may contribute to myocardial dysfunction in the absence of coronary artery atheroma.<sup>2</sup> This is also sustained by the fact that patients with diabetes, independently of the severity of coronary artery disease, have increased risk of heart failure in comparison with subjects without diabetes.<sup>3,4</sup>

In 1972 for the first time in medical history, the description of 4 patients with diabetes and heart failure but without arterial hypertension or coronary artery disease appeared. The anatomical dissection of their hearts revealed LV hypertrophy and fibrosis without evidence of coronary artery atheroma or another substrate pathology responsible for these findings. This clinical entity (disease) was considered as independent and was baptized “diabetic cardiomyopathy” (DCM).<sup>5</sup>

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The aim of this review is to provide up-to-date information on the pathophysiology, diagnosis, and management of DCM. We performed a comprehensive search in the PubMed and Embase databases up to February 2010 using the following keywords alone and in combination to retrieve available literature data: “diabetes mellitus”, “cardiomyopathy”, “cardiac myocytes,” “pathophysiology”, “hyperglycemia”, “insulin resistance”, “risk factors”, “myocardial performance”, “diastolic dysfunction”, “heart failure”, “diagnosis”, and “treatment”. All types of articles (randomized controlled trials, original studies, review articles, and case reports) in humans and animals published in English language were included. Publications were studied in detail.

## Epidemiological data on DCM

Epidemiological evidence has demonstrated worldwide that macrovascular complications (coronary artery disease, peripheral vascular disease, and stroke) are more common (2–4 times) among diabetes patients in comparison with the nondiabetes subjects. This is valid for both type 1 and type 2 diabetes even when all other cardiovascular risk factors, such as hypertension, obesity, smoking, dyslipidemia, age, and sex, are taken into consideration.<sup>6</sup>

The Framingham Study showed that the frequency of coronary artery disease is twice more common in diabetes patients of both sexes, since women with diabetes appear to lose their normal premenopausal protection against cardiovascular disease. Moreover, death from coronary artery disease is 3 times more common in diabetes patients compared with nondiabetes subjects matched by age and sex. In other words, a patient with diabetes is not only at high risk of developing coronary artery disease, but furthermore, he is more susceptible to a worse prognosis.<sup>4</sup> Atheromatous lesions have an earlier onset, faster development, and greater density in diabetes.<sup>7</sup> The risk of coronary artery disease increases rapidly after the age of 40 in patients with type 1 diabetes, and by the age of 55, 35% of the patients of both sexes have died because of a coronary artery event, compared with 8% of men and 4% of women in the general population.<sup>8</sup>

It should be noted that in the last 30 years, the substantial decrease in cardiovascular mortality in men without diabetes (up to 36.4%) was not followed by a decrease in the cardiovascular mortality among the male diabetic population (up to 13.1% decline). Even more disappointing were the results among women. Although cardiovascular mortality in women without diabetes was reduced by 17%, it was increased by 23% in the female diabetic population.<sup>9</sup> This supports even further the loss of the premenopausal protection

against coronary artery disease in diabetes seen in healthy women. The STENO-2 Study demonstrated that in patients with type 2 diabetes, even when all associated cardiovascular risk factors are treated and the incidence of cardiovascular events is decreased by 50%, the cardiovascular mortality still remains high.<sup>10</sup>

In one prospective study that included a population of 1,059 patients with diabetes and 1,373 subjects without diabetes, who were followed up for at least 7 years, it was concluded that the frequency of mortality in patients with diabetes but without myocardial infarction was similar to that in subjects without diabetes but with myocardial infarction.<sup>11</sup> Moreover, in patients with diabetes and acute myocardial infarction, mortality during the first month is above 42%, whereas in subjects without diabetes, it is less than 20%.<sup>12,13</sup> Some studies have demonstrated that good glycemic control is associated with higher survival rates after acute myocardial infarction.<sup>14</sup> In diabetes subjects with angiographically proven coronary artery disease, the survival rates are decreased by 30% compared with their nondiabetes counterparts.<sup>15</sup> Diabetic nephropathy, which often coexists, especially proteinuria, increases further the risk of cardiovascular death.<sup>16</sup> Moreover, a significant association between idiopathic cardiomyopathy and diabetes was recently described.<sup>17</sup>

An important consequence of DCM is heart failure, which is more common in people with diabetes and complicates acute myocardial infarction more often than in the nondiabetic population. The increased percentage of patients with diabetes and heart failure in numerous multicenter epidemiological studies is in contrast to the total diabetic burden in the general population (6%–8%). In the Studies of Left Ventricular Dysfunction (SOLVD), the percentage of patients with diabetes and heart failure was up to 26%,<sup>18</sup> whereas in the Assessment Trial of Lisinopril and Survival (ATLAS) study, it was 19%<sup>19</sup> and in the Vasodilator-Heart Failure Trial II (V-HeFT II), it was up to 20%.<sup>20</sup>

These findings are in agreement for the presence of an additional detrimental factor in the diabetic myocardium, which predisposes it to extensive damage followed by heart failure. Even more, they are supportive for the early treatment of diabetes patients with aspirin and other measures that are used for secondary prevention in the general population, even in the absence of clinically apparent macrovascular complications.

In summary, cardiovascular disease is 2–3 times more common, and survival is worse in subjects with diabetes in comparison with age-matched and sex-matched counterparts.

The prevalence of heart failure with preservation of systolic function among patients with diabetes is 19%–26%.

## Definition of DCM

DCM is defined as the cardiovascular damage present in diabetes patients, which is characterized by myocardial dilatation and hypertrophy, as well as a decrease in the systolic and diastolic function of the left ventricle, and its presence is independent of the coexistence of ischemic heart disease or hypertension. DCM may be subclinical for a long time, before the appearance of clinical symptoms or signs. According to the molecular theory of DCM, hyperglycemia is the main pathogenetic factor, which causes abnormalities at the cardiac myocyte level, eventually leading to structural and functional abnormalities.<sup>21</sup>

## The pathophysiological substrate of DCM

### The anatomical damage of the myocardial substrate

Atheromatous plaques in patients with diabetes are not qualitatively different from those affecting the nondiabetic population. However, atheroma in patients with diabetes is more extensive, is more diffuse, and involves distal vessels in both the coronary and peripheral circulation.<sup>22</sup> Pathologic anatomical alterations of the small coronary vessels and the myocardial endothelium include increased cell adhesiveness, impaired relaxation, impaired fibrinolysis, and increased permeability.<sup>22</sup> The early stages of DCM are dominated by the pathological alterations in the myocardial interstitium, ie, formation of nonenzymatic advanced glycation end products (AGEs), impaired compliance, and ischemia from the disease in the vasa vasorum. The morphology of the myocardial cells and small coronary vessels is anatomically preserved. These alterations lead to impaired myocardial contractility.<sup>23</sup> As the disease progresses, LV hypertrophy appears as a result of the hypertrophy of the myocardial cells, the interstitial and perivascular fibrosis, the greater thickening of the capillary basement membrane, and the formation of microaneurysms in small capillary vessels. This ultimate observation may be the actual pathophysiological connection between diabetes microvascular and macrovascular disease.<sup>24</sup>

## Structural alterations leading to ventricular dysfunction

Medial layers of arterioles throughout the cardiac circulation in diabetes show “hyaline” change, an amorphous, ground

glass appearance, resulting from breakdown of structural proteins (largely thought to be collagen) and the uptake of glycated plasma proteins into the vessel wall. Similar changes are seen in older nondiabetic subjects as part of the aging process and in hypertension. The reduced blood supply resulting from microvascular disease and affecting the vasa vasorum in diabetes further damages the small and medium arterioles of the diabetic heart. A clear relationship between the loss of cardiac function and the histological damage in the diabetic blood vessels is very difficult to demonstrate. However, it is plausible that the structural changes and loss of elasticity contribute to hypertension and possibly to the greatly increased risk of macrovascular events in diabetes. The European Heart Association’s Guidelines (2009) have defined LV hypertrophy as an increase in LV mass index above 125 g/m<sup>2</sup> for men and above 110 g/m<sup>2</sup> for women. The Framingham Study demonstrated that the determination of LV hypertrophy electrocardiographically was not associated significantly with increased cardiovascular morbidity and mortality.<sup>25</sup> However, in the Framingham Study, when LV hypertrophy was assessed echocardiographically in a population of 3,222 patients, it was demonstrated that the relative risk for cardiovascular mortality for each 50 g/m<sup>2</sup> increase of the LV mass above the normal limits was equal to 1.49 for men and 1.57 for women.<sup>26</sup>

LV hypertrophy is significantly associated with an increase in markers of systemic inflammation, such as fibrinogen, C-reactive protein, and microalbuminuria. In one study including 1,299 patients with type 2 diabetes, microalbuminuria not only was a marker of endothelial dysfunction and increased risk of atherosclerosis but also was positively associated with LV mass.<sup>27</sup>

## Functional alterations of DCM

Uncomplicated reduction of systolic myocardial functioning is defined as the loss of the heart’s ability to pump arterial blood in the peripheral circulation. However, the elementary difference between the uncomplicated reduction of systolic myocardial function and systolic heart failure is that in the latter, the clinical symptoms and signs of heart attack appear as a result of the former. Thus, the main guidance point of systolic myocardial dysfunction is the reduction of the LV ejection fraction.

However, recent studies revealed that the classical 2-dimensional echocardiography (2DE) may not be able to detect and diagnose the early uncomplicated reduction of the LV systolic myocardial functioning. This is due to the fact that classical 2DE can determine only LV

circumferential function and cannot estimate LV longitudinal functioning.<sup>28</sup>

In DCM, progression and appearance of reduction of systolic function is slow, often when patients have already developed a significant reduction of diastolic myocardial functioning. The prognosis of patients with LV systolic myocardial dysfunction is poor, and the percentage of annual mortality is equal to 15%–20%.

Diastole is defined as the period when the myocardial muscle generates effort and energy, while in mechanical (isovolumic deceleration and relaxation phase) and electrophysiological inactivity (automatic depolarization).<sup>29</sup> Reduction of diastolic myocardial functioning is determined by a delayed and extended diastolic phase. Diastolic dysfunction is also characterized electrophysiologically by the prolongation of the active dilatation and the augmented passive stiffness of the left ventricle, which portray the passive diastolic LV compliance in heart failure.<sup>30</sup> Impaired diastolic functioning of the left ventricle appears in 27%–69% of the cardiovascular asymptomatic population with diabetes<sup>31</sup> and is responsible for the 30% of the patients ending up with diabetes and clinical symptomatic heart failure.<sup>32</sup> Impaired diastolic compliance and maintenance of the systolic function is usually the initial heart lesion in the progression of DCM.<sup>33</sup> Failure of diastolic relaxation of the left ventricle leads to impaired filling and reduced cardiac reserve on exercise. In spite of the absence of systolic dysfunction, numerous clinical studies have demonstrated a decreased ejection fraction, which determines reduced cardiac residual reserve in asymptomatic patients with diabetes.<sup>34</sup> Subclinical DCM characterized by reduced cardiac residual reserve can develop into a significant clinical entity, especially when myocardial ischemia coexists or suddenly appears.

Diastolic myocardial function can be evaluated by cardiac catheterization for the evaluation of the isovolumic relaxation rhythm and the LV isovolumic contraction time.<sup>35</sup> This method, although highly accurate, for the evaluation of LV diastolic function is invasive and has increased possibilities of accidental injury. The alternative noninvasive techniques include classical 2DE and M-mode echocardiography with Doppler. LV diastolic functioning can also be evaluated by controlling the transmitral and pneumocardial blood flow.<sup>36</sup>

The medical term “diastolic dysfunction” refers exclusively to the echocardiographic finding of an abnormal LV deceleration and relaxation time, without the coexistence of any clinical evidence suggestive of heart failure. However, diastolic heart failure is defined as the clinical syndrome of heart failure with preservation of a normal LV ejection

fraction. Echocardiographic findings of isolated myocardial dysfunction, such as subclinical reduction of myocardial diastolic compliance and loading, are reliable prognostic markers of future chronic heart failure.<sup>37</sup> Moreover, patients with diastolic heart failure have increased cardiovascular mortality (equal to 5%–8%) compared with healthy subjects matched by age and sex (equal to 1%).<sup>38–40</sup>

The impact of diastolic dysfunction is associated with good glycemic control, as assessed by hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) levels.<sup>41</sup> Possibly, the main cause for this relationship are the increased circulatory AGEs<sup>42</sup> and the increased production of free oxygen radicals,<sup>43</sup> resulting in an increased accumulation of collagen in the myocardium and in myocardial fibrosis.<sup>44,45</sup>

Coexistent hypertension accelerates the functional underlying process, leading to LV hypertrophy, systolic ventricular dysfunction, and greatly increased risk of congestive heart failure. Although, it is difficult to disentangle the effects of hypertension from the other facets of the pathophysiology of ventricular dysfunction in diabetes, LV hypertrophy has also been observed in nonhypertensive individuals with diabetes, and particularly in women.<sup>46</sup>

In conclusion, DCM is characterized by LV hypertrophy and myocardial dilatation, which lead to LV diastolic and systolic dysfunction. These are related to diabetic fibrosis, inflammation, ischemia, and presence of microvascular complications. DCM is independent of the coexistence of ischemic heart disease or hypertension.

## The molecular substrate of DCM

Hyperglycemia causes significant functional alterations to the cellular Na<sup>+</sup>–Ca<sup>2+</sup> ionic channel, resulting in a decreased extrapolation and an increased intracellular concentration of ionic calcium. Moreover, in diabetes, a dysfunction of the cellular Na<sup>+</sup>–K<sup>+</sup> ionic channel appears, which primarily causes an increase in the intracellular sodium concentration and secondarily an additional increase to the already augmented intracellular calcium concentration in the diabetic cardiac myocytes.<sup>47</sup>

Dyslipidemia and increased production of free oxygen radicals<sup>48,49</sup> may cause metabolic alterations to the genetic transcription factors and coding.<sup>50,51</sup> The result of these alterations is a modification in the translation of nucleoprotein genes, such as RAS and insulin-like growth factor 1 (IGF-1), responsible for the myocardial substrate and myocardial fiber structure and also for the maintenance of a normal myocardial compliance.<sup>52,53</sup> Accordingly, increased expression of the early cardiopathology-related gene RAS predisposes to

insulin resistance, whereas the IGF-1 increases myocardial contractility through an increase of the intracellular calcium accumulation and by intensifying the sensitivity of the cardiac myofibers to the circulatory calcium concentration.<sup>54</sup> IGF-1 is present in the cardiac myocytes, and its expression is augmented by decreased insulin concentration, increased mechanical stress, and increased peripheral vascular resistance. IGF-1 acts synergically with angiotensin II in promoting cellular development. As a result, this leads to myocardial hypertrophy of the diabetic heart ventricle mass even when blood pressure levels are within the normal range.<sup>55</sup>

Thus, hyperglycemia, dyslipidemia, and increased production of free oxidant radicals are main metabolic pathogenetic risk factors leading to DCM.

## The interplay of cardiac autonomic neuropathy in DCM

Cardiac autonomic neuropathy (CAN) is a common complication of diabetes, causing abnormalities in heart rate control and in central and peripheral vascular dynamics. CAN affects almost 17% of the patients with type 1 and 22% of those with type 2 diabetes. An additional 9% of patients with type 1 and 12% of those with type 2 diabetes have milder forms of autonomic dysfunction.<sup>56</sup>

Several studies have confirmed that cardiac neuropathy has the propensity to cause a reduction in the cardiac ejection fraction, impair systolic dysfunction and decrease diastolic filling, thus having an important contribution to the deterioration of diastolic myocardial function and DCM. Abnormalities of LV diastolic filling are overstated in patients with diabetes and CAN in comparison with patients with diabetes but without this complication.<sup>57</sup> When LV function was assessed in a diabetic population by resting and exercise radionuclide ventriculography, an abnormal LV performance was revealed in 37% of the patients included in the study. CAN was present in 59% of the subjects with DCM, a significantly increased incidence compared with that of 8% in the patients without this complication. Moreover, there were significant reductions in the ventricular ejection fraction at rest and with maximal exercise in patients with CAN compared with those without this complication.<sup>58</sup>

In a population of subjects with type 1 (insulin-dependent) diabetes, a decrease of the diastolic myocardial function to 21% was also demonstrated. None of the patients included in the study had clinical evidence of coronary artery disease, and diastolic myocardial dysfunction (impaired diastolic

LV filling) was significantly associated with the presence of CAN.<sup>59</sup>

CAN is portrayed by a significant reduction in heart rate variability and an alteration in the parasympathetic–sympathetic balance, in which a reduction in parasympathetic tone secondary to autonomic neuropathy leads to a relative overactivity of the sympathetic system. Patients with diabetes and mild CAN have been shown to have distal LV sympathetic denervation, whereas patients with severe CAN have a pattern of distal sympathetic denervation associated with proximal ventricular islands of hyperinnervation. These areas of denervation and hyperinnervation may cause unstable regions of electrical, vascular, or autonomic heterogeneity conducive to DCM.<sup>60</sup>

Numerous studies have demonstrated a significant correlation between dysfunction of the parasympathetic nervous system activity and impaired myocardial function. One study evaluated the role of parasympathetic nervous system activity in cardiovascular performance on a group of clinically asymptomatic type 2 diabetes patients, ie, without any symptom, sign, or objective measurement of ischemia or cardiomyopathy. Although patients with CAN corresponded positively to the increase in oxygen uptake by an equivalent percent increase in cardiac output, this response was significantly reduced compared with that of patients without CAN. Thus, it was shown that impaired sympathetic and parasympathetic responses, which normally augment cardiac output and redirect peripheral blood flow to skeletal muscles during exertion, may limit exercise tolerance.<sup>61</sup>

The relationship between parasympathetic nervous dysfunction and DCM was confirmed by an important decrease of heart rate variability during deep breathing maneuver in subjects with type 1 diabetes and by the presence of pathological echocardiographic findings of the LV filling rhythm.<sup>62</sup>

Dysfunction of the sympathetic nervous system activity has been associated with a decrease in both systolic and diastolic myocardial function in subjects with type 2 diabetes.<sup>63</sup> A significant association between a decrease of the transmitral ratio of early to late peak mitral filling wave velocities and the augmentation of sympathetic myocardial neurosis has also been demonstrated.<sup>64</sup> This relationship has confirmed that in DCM, the abnormal cardiac sympathetic neurosis contributes to the abnormal LV filling. The transmitral ratio of early to late peak mitral filling has also been associated with orthostatic hypotension as a clinical manifestation of CAN.<sup>46</sup> Moreover, the same index of abnormal cardiac filling was associated with an abnormal expiration/inspiration ratio, ie, an index of parasympathetic dysfunction in patients with

type 1 diabetes and CAN.<sup>65</sup> Finally, CAN is associated with a decrease of the elastic vascular properties and an increase of peripheral vascular resistance due to the augmentation of the sympathetic nervous tone.<sup>66</sup>

Resting tachycardia reduces the heart's ability to pump blood in the peripheral circulation and interferes with the ventricular chambers' capacity to fill with blood properly. Ventricular tachycardia not only reduces the time of ventricular filling but also interferes with the timely atrial contraction. When the heart's labor capacity is greatly reduced for a prolonged period, cardiac arrest and death are likely to happen.<sup>67</sup> Through predisposition to arrhythmias, CAN may lead to LV dysfunction followed by sudden death.<sup>68</sup> Recent studies revealed that classical<sup>69,70</sup> and newer markers of arrhythmogenicity<sup>71</sup> are increased in subjects with diabetes and CAN in comparison with subjects with diabetes but without this complication. Moreover, one recent study revealed that increased markers of spatial ventricular heterogeneity in type 2 diabetes subjects and CAN are associated with the structural and functional properties of the myocardium.<sup>71</sup>

In conclusion, CAN is strongly and independently associated with the structural and functional pathogenetic substrate of DCM in both type 1 and type 2 diabetes patients. This is partially explained by the significant reduction in heart rate variability present in autonomic neuropathy, and an alteration in the parasympathetic–sympathetic balance of the heart, leading to parasympathetic reduction and sympathetic overactivity.

## Risk factors for DCM

### Hyperglycemia

Hyperglycemia could contribute to macrovascular disease through various mechanisms. Hyperglycemia causes significant functional alterations to the cellular  $\text{Na}^+/\text{Ca}^{2+}$  ionic channel, resulting in a decreased extrapolation and an increased intracellular concentration of ionic calcium. Moreover, in diabetes, a dysfunction of the cellular  $\text{Na}^+/\text{K}^+$  ionic channel appears, which primarily causes an increase in the intracellular sodium concentration and secondarily an additional increase to the already augmented intracellular calcium concentration in the diabetic cardiac myocytes.<sup>47</sup> However, the most convincing pathogenetic mechanism of hyperglycemia is via the formation of AGEs. AGEs cross-link vessel wall proteins, therefore causing thickening and leakage of the vasculature and forming irreversible and abnormal deposits of plasma-derived proteins in the myocardial subintimal arterial layers.<sup>72</sup> Furthermore, AGEs generate toxic reactive oxygen species (ROs) that impair cellular interactions and

damage myocardial vascular function, causing endothelial vasomotor dysfunction.<sup>73</sup>

Some of the effects of AGEs are mediated through specific receptors (RAGE) expressed by vascular endothelial, smooth muscle cells and cardiac myocytes. In the cardiac endothelium, AGE–RAGE interaction leads to upregulation of procoagulant and adhesive proteins, including tissue factor, plasminogen activator inhibitor 1 (PAI-1), and vascular cell adhesion molecule 1 (VCAM-1). Expression of VCAM-1 results in an increase in monocyte adhesion, while monocytes expressing RAGE are recruited by chemotaxis to sites of AGE accumulation. There they infiltrate the myocardial subendothelium to form foam cells, an early step in atherogenesis. Other extracellular RAGE ligands are the RAGE-binding proteins that interact with RAGE on cardiac myocytes to induce expression of tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ), VCAM-1, nuclear factor  $\kappa$ B (NF- $\kappa$ B), and interleukin 1, thus modulating the inflammatory component of cardiovascular disease through the cytokine cascade.<sup>74</sup>

A strong relationship between glycemic control and DCM has been demonstrated in major multicenter prospective studies. The Diabetes Conventional and Complications Trial (DCCT) showed that patients with diabetes who are conventionally treated have a nearly double incidence of DCM when compared with patients with diabetes who are intensively treated. Among the risks for DCM, beyond glycemic control, were increased levels of serum cholesterol and triglycerides.<sup>75</sup> For each 1% reduction in  $\text{HbA}_{1c}$ , the United Kingdom Prospective Diabetes Study (UKPDS) demonstrated a 14% reduction in myocardial infarction.<sup>76</sup> Moreover, impaired glucose tolerance has been identified as a risk factor for DCM, suggesting that even mild hyperglycemia may contribute to DCM.<sup>77</sup>

## Insulin resistance and the metabolic syndrome

Insulin resistance and hyperinsulinemia have been identified as risk factors for DCM.<sup>78,79</sup> In hyperinsulinemia and insulin resistance, an imbalance in the direct effects of insulin action occurs, accompanied by the confounding effects of other cardiovascular risk factors associated with the insulin resistance syndrome, ie, central obesity, hyperglycemia, hypertriglyceridemia, low high-density lipoprotein (HDL), and hypertension.<sup>80</sup> The clustering of these cardiovascular and atherothrombotic risk factors that accompany insulin resistance provides a plausible basis for DCM and is often associated with adverse cardiovascular effects.<sup>81,82</sup> Hyperinsulinemia and insulin resistance are also associated

with a cluster of thrombotic risk factors, such as elevated levels of PAI-1,<sup>83,84</sup> factor VII, factor XII, and fibrinogen.<sup>85–87</sup> Increased levels of factor VII and XII may also occur through activation by triglyceride-rich particles, whereas hyperfibrinogenemia may be attributed to smoking, increased body mass, and inflammatory responses.

Insulin resistance is often associated with a combination of established and emerging risk factors, including hypertension and C-reactive protein.<sup>88,89</sup> C-reactive protein is an acute-phase inflammation marker that has been associated with an increased risk for DCM.<sup>90,91</sup> Recent studies have confirmed the association between increased levels of C-reactive protein and worse LV myocardial performance, as well as risk factors for atherosclerosis and cardiovascular disease in subjects with metabolic syndrome (MetS).<sup>92</sup> MetS status per se was found to be the strongest predictor of cardiomyopathy, thus implying that the clustering of the metabolic disturbances has additional prognostic information than its individual components in terms of myocardial performance and may explain in part the excess cardiovascular risk present in the MetS.<sup>92</sup>

In conclusion, the effects of insulin on the diabetic heart are related to both systemic metabolic abnormalities and the direct effects of insulin action on the vasculature. Although, the elevation and the imbalance of the cardiovascular and atherothrombotic metabolites and cytokines related to hyperinsulinemia and insulin resistance have a crucial contribution in the pathogenesis of DCM, it should be noted that the direct action of insulin on the vasculature has also been proposed to mediate a combination of proatherogenic and antiatherogenic effects related to endothelial function and smooth muscle cell growth.<sup>93</sup> The importance of insulin resistance and the MetS is further confirmed by the fact that insulin-resistant individuals who are either hyperinsulinemic and normoglycemic<sup>79</sup> or hyperinsulinemic with impaired glucose tolerance<sup>94</sup> show a similarly high-risk profile to those with overt diabetes, whereas others who are destined to develop diabetes, but lack insulin resistance, are not at increased risk.<sup>81,95</sup>

## Dyslipidemia

Increased atherogenesis and insulin resistance in diabetes and MetS have been attributed in large part to a proatherothrombotic dyslipidemia, related to hypertriglyceridemia, elevated very low-density lipoprotein, and decreased HDL cholesterol levels.<sup>96,97</sup> Insulin resistance results in increased levels of triglyceride-enriched, small, dense low-density lipoprotein (LDL) particles, which have been associated with an increased risk of ischemic heart disease.<sup>98</sup> Moreover,

the combined elevation of fasting insulin, apoprotein B, and small, dense LDL particles has been identified as a nontraditional risk factor cluster for coronary artery disease.<sup>99</sup> Dyslipidemia has been recently associated with worse myocardial performance in type 2 diabetes subjects<sup>100</sup> and in the MetS.<sup>92</sup> Additional risk factors for DCM associated with dyslipidemia include increased lipoprotein(a)<sup>101</sup> and nonesterified fatty acids.<sup>102</sup>

## Hypertension

Hypertension commonly coexists with type 1 and type 2 diabetes. Hypertension per se is a major risk factor for vascular complications, ie, myocardial infarction and stroke.<sup>103,104</sup> According to major multicenter studies, the majority (almost 50%) of patients with diabetes and no clinical evidence of atheromatous disease are hypertensive or are taking antihypertensive drugs. In diabetes subjects with DCM, the prevalence of hypertension is even higher.<sup>105</sup> Insulin resistance has been proposed to be the fundamental cause of hypertension and DCM in type 2 diabetes.<sup>106</sup> Acquired factors such as obesity and physical inactivity may also contribute. Hypertension is an important feature of the cluster of the cardiovascular risk factors included in the MetS. The relationship between these metabolic components is complex and in part largely unexplained. Insulin resistance could raise blood pressure by the loss of insulin's normal vasodilator activity,<sup>107</sup> or through effects of the accompanying hyperinsulinemia. These include Na<sup>+</sup> and water retention, increased intracellular Na<sup>+</sup> concentrations<sup>108</sup> that enhance the contractility and stimulate proliferation of vascular smooth muscle,<sup>109</sup> increase peripheral resistance, and cause sympathetic overactivity.<sup>110</sup> In other words, hypertension and DCM are synergic and share similar pathogenetic pathways. The characteristic dyslipidemia of insulin resistance that contributes to DCM may also contribute to hypertension, as small, dense LDL particles are especially susceptible to oxidation, and oxidized LDL can suppress endothelial nitric oxide production and so promote vasoconstriction; hypertriglyceridemia also impairs endothelium-dependent vasorelaxation.<sup>111</sup> Studies have shown that fibrates used to treat hypercholesterolemia also reduce the prevalence of hypertension up to 25%.<sup>112</sup>

## Obesity

Obesity predisposes to type 2 diabetes, hypertension, dyslipidemia, and ultimately atheroma, which is one of the major causes of premature death in obese people.<sup>113</sup> Obesity is recognized as an independent cardiovascular risk factor.<sup>114</sup> Central obesity is characterized by excess fat deposited

both subcutaneously around the abdomen and within the visceral cavity and is commonly found in patients with type 2 diabetes and MetS. Central obesity is associated with insulin resistance and proinflammatory responses that cause glucose intolerance and a highly atherogenic-risk profile. Adipose tissue produces nonesterified fatty acids and cytokines such as TNF- $\alpha$  that may contribute to both insulin resistance and atherogenesis. Reduced levels of adiponectin, an insulin-sensitizing protein whose secretion by adipose tissue is paradoxically decreased in obesity, may also contribute to insulin resistance and DCM.<sup>115</sup> Indeed, in a recent study, central obesity, as part of the MetS, was significantly and independently associated with LV myocardial dysfunction.<sup>116</sup>

### The effect of diabetic nephropathy

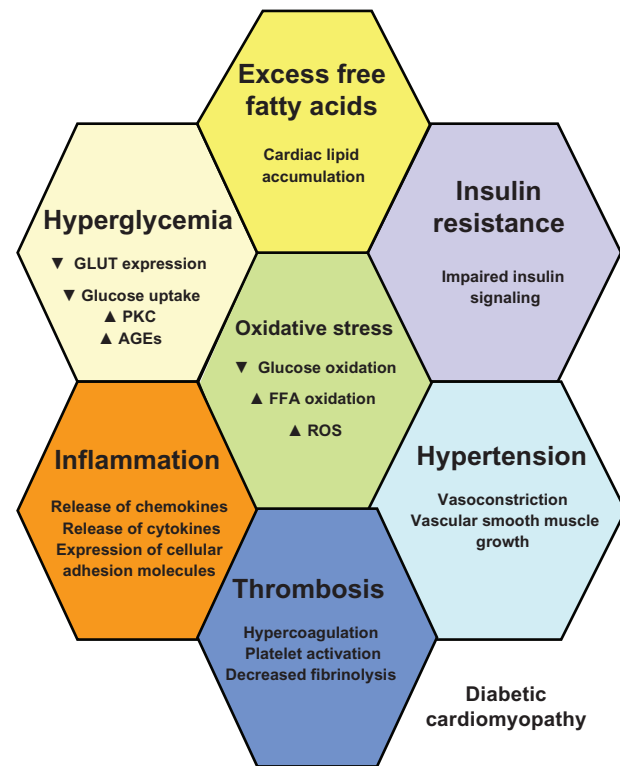
Nephropathy is a common complication affecting almost one-third of patients with diabetes.<sup>117</sup> Both microalbuminuria (albumin excretion rate of 30–299 mg/24 h) and proteinuria (albumin excretion, >300 mg/24 h) are markers of increased cardiovascular risk.<sup>118,119</sup> In type 1 diabetes, the relative risk of DCM is 1.2-fold in patients with microalbuminuria<sup>120</sup> and 10-fold in patients with proteinuria<sup>121</sup> compared with patients with normoalbuminuria. In type 2 diabetes, the risk of DCM is increased 2- to 3-fold in microalbuminuria<sup>122</sup> and 9-fold in proteinuria.<sup>123</sup>

The onset of microalbuminuria is associated with an excess of cardiovascular risk factors, including hyperglycemia, dyslipidemia, and numerous prothrombotic and atherogenic changes.<sup>124,125</sup> Moreover, there is growing evidence that the genetic susceptibility influences the development of diabetic nephropathy and also affects the diabetic cardiovascular system.<sup>126</sup> Suggested mechanisms linking renal and cardiovascular disease include endothelial dysfunction, abnormalities of the renin–angiotensin system, and widespread vascular basement membrane defects.

In conclusion, the pathogenic contribution to the development of DCM includes insulin resistance, increased formation of AGEs, MetS, hyperglycemia, dyslipidemia, obesity, and presence of microangiopathy. Their interplay is complex, since they can act in parallel and synergically and, at the same time, have a cause and effect result. Thus, they should be equally predicted and effectively treated. The contribution of the various factors in the development of DCM is depicted in Figure 1.

### The diagnostic paths through DCM

Echocardiography is a reliable, noninvasive technique for the determination of LV hypertrophy and the reduction of both



**Figure 1** The pathophysiological substrate of diabetic cardiomyopathy: in diabetes, hyperglycemia, excess free fatty acid (FFA) release, and insulin resistance, engender adverse metabolic events that affect the cardiac myocytes. Hyperglycemia is associated with decreased glucose transportation (GLUT), uptake, and oxidation, as well as increased formation of advanced glycation end products (AGEs) and increased activation of protein kinase C (PKC). Excess FFA release is followed by cardiac lipotoxicity, ie, increased cardiac lipid accumulation and increased generation of reduced reactive oxygen species (ROS) at the level of the electron transport chain. Together with insulin resistance and impaired insulin action and signaling, these metabolic paths augment vasoconstriction, produce and further aggravate arterial hypertension, increase inflammation with liberation of leukocyte-attracting chemokines, increase production of inflammatory cytokines, and augment expression of cellular adhesion molecules. Thrombosis is further promoted, together with platelet activation.

systolic and diastolic myocardial function. Moreover, it has a prognostic value for the early diagnosis of DCM.

### The classical echocardiographic markers of DCM: advantages and disadvantages

Early deteriorations of myocardial function are characterized by a normal ejection fraction and a decrease in ventricle filling during the initial phase of diastole. Prolongation of isovolumic myocardial relaxation and an increase in atrial filling further confirm a decrease in diastolic myocardial function. The Framingham study showed an increase of LV mass in women with diabetes, independent of the effects of other traditional risk factors.<sup>46</sup> Subsequent studies confirmed these results in both genders, highlighting associations of both diabetes and glucose intolerance with LV structure abnormalities, independent of the influence of relevant covariates, such as arterial blood pressure levels



and treatment with angiotensin-converting enzyme (ACE) inhibitors.<sup>43,127–130</sup> The same was true for patients with type 1 diabetes.<sup>131</sup> Early echocardiographic studies revealed that half of the diabetic population with decreased myocardial diastolic function remain undiagnosed with the classical echocardiographic techniques. This is due to the fact that the echocardiographic subestimation of the degree of diastolic dysfunction with the classical echocardiographic markers in the subjects with normal arterial blood pressure levels is equal to 60%.<sup>132,133</sup>

### The newest echocardiographic markers: their performance structure and role as diagnostic tools

Total ejection isovolumic (TEI) index is a myocardial performance index and a method for the global estimation of the LV performance.<sup>134</sup> The TEI index is not influenced by the increased left atrial loading pressure often present in the advanced stages of diastolic heart failure, which is a key advantage compared with the classical echocardiographic methods.<sup>135,136</sup> The isolated estimation of the decrease in diastolic myocardial function has been recently questioned owing to the presence of reduced systolic function in patients with normal ejection fraction. Therefore, evaluation of TEI index may become a valuable tool for the early diagnosis of upcoming myocardial ischemia.<sup>137</sup>

An important limitation of the single use of TEI index for the estimation of myocardial dysfunction is that it does not allow the evaluation of the pathogenetic substrate of myocardial dysfunction because it cannot evaluate the myocardial pressure levels during diastolic filling or the changes in systolic preload.<sup>138</sup> However, the clinical significance of TEI index as a diagnostic tool for New York Heart Association Grade I–III heart failure was recently successfully demonstrated and was identical when compared with the results of invasive techniques.<sup>139</sup> Moreover, TEI index was demonstrated as a significant prognostic marker of cardiovascular morbidity and mortality in elderly patients, independent of the coexistence of the classical cardiovascular risk factors.<sup>140</sup>

In a recent study in type 2 diabetes patients without macrovascular complications, TEI index was significantly and independently associated with the presence of DCM.<sup>100</sup> Moreover, in type 2 diabetes patients with DCM, higher values of the TEI index were associated with increased ventricular arrhythmogenicity, suggesting a significant association between the underlying LV diastolic dysfunction and the LV electrophysiological activity of the diabetic heart. This

association was further supported by the findings of another study in a nondiabetic population with MetS, where worse myocardial function, assessed by higher TEI index values, was associated with increased ventricular arrhythmogenicity.<sup>92</sup> This study concluded that the electrophysiological abnormalities present in the MetS may be due to the direct effects of hyperinsulinemia on myocardial membrane activity or the electrophysiological alterations that accompany the biochemical and functional abnormalities caused by the shift in the myocardial substrate utilization.<sup>141</sup>

MetS was also associated with worse myocardial performance assessed by the TEI index in a population without diabetes, hypertension, or other macrovascular complications. This association was confirmed for the MetS per se, the sum of its components and its particular components. Additionally, it was demonstrated that factors associated with conditions commonly associated with MetS, such as insulin resistance, low-grade inflammation, and microalbuminuria, were also associated with worse LV myocardial performance.<sup>116</sup>

Other modern echocardiographic techniques, such as transmitral pulsed Doppler and its applications (strain and strain rate), which are less susceptible to the alterations of the cardiac loading conditions, have recently demonstrated 63% sensitivity against the 50% of the pulsed Doppler in diagnosing DCM.<sup>137,142–144</sup> Table 1 shows the main echocardiographic findings and the incidence of DCM in major and recent studies.

### Treatment strategies of DCM: risk factors, management and lessons from studies

#### Lifestyle

Regular physical exercise and limitation of fat and total energy intake remain the cornerstone of the management of overweight diabetes patients who currently represent 80% of type 2 and at least 25% of type 1 diabetes patients worldwide. Patients with diabetes should be encouraged to undertake moderate aerobic activity, ie, walking for 30–45 min everyday. Patients with angina or breathlessness on exertion should exercise within their limitations, aiming gradually to increase their activity. In obese patients with a body mass index (BMI) > 30 kg/m<sup>2</sup>, an initial target should be 10% weight loss; in those who are not obese, a target BMI of ≤25 kg/m<sup>2</sup> may be reasonable.

One prospective, randomized, controlled study evaluated the effects of diet and exercise on the reduction of the overall incidence of DCM in patients with type 2 diabetes for a follow-up period of 6 years. Subjects were randomized either

**Table 1** Main and recent echocardiographic, population-based studies on diabetic cardiomyopathy

Reference	Population sample	Findings	Incidence of DCM
[46]	1,986 men + 2,529 women (111 with DM + 381 with IGT)	↑ LV wall thickness, ↑ relative wall thickness, ↑ LV end-diastolic dimension, ↑ LV mass	13.9% in men 16.1% in women
[127]	5,201 men + women (2,697 with DM or IGT, age ≥ 65 years)	↑ ventricular septal thickness, ↑ posterior wall thickness, ↑ left ventricular mass, ↑ early and late diastolic transmitral peak flow velocities	40% in both sexes
[43]	1,810 men + women with DM	↑ LV mass, ↑ LV wall thicknesses ↓ LV fractional shortening, ↓ midwall shortening, ↓ stress-corrected midwall shortening	14% in women 12% in men
[128]	1,950 men + women with HTN (386 with DM)	↑ LV mass, ↑ LV relative wall thickness, concentric LV geometry, ↓ LV stress-corrected midwall shortening, ↓ myocardial function (↓ midwall and ↓ stress-corrected midwall fractional shortening)	38% in both sexes
[129]	3,628 men + women (457 men + women with IGT)	↑ LV mass, ↑ cardiac index, ↑ LV wall thicknesses and ↑ relative wall thickness	12.6% in both sexes
[130]	173 men + women with DM + HTN	↑ LV mass	30% in both sexes
[131]	39 boys + girls with type 1 DM	↑ LV mass, ↓ LV performance	30% in both sexes
[100]	148 men + women (74 with DM)	↑ LV mass index, ↑ TEI index	34% in both sexes
[92]	306 men + women (153 with MetS)	↑ LV mass index, ↑ TEI index	12% in both sexes
[116]	550 men + women (275 with MetS)	↑ TEI index	18% in both sexes
[142]	186 type 2 diabetes patients with normal ejection fraction	Systolic dysfunction: ↓ peak strain and ↓ strain rate ↑ calibrated IB (myocardial reflectivity)	15.8% in both sexes
[143]	41 diabetes patients with normal resting LV function and a normal dobutamine echo	↓ peak myocardial systolic velocity ↓ early diastolic velocity	16% subtle dysfunction in both sexes
[137]	35 type 2 diabetes patients	↓ longitudinal peak systolic velocity at rest and at peak stress, ↓ functional reserve, ↑ radial systolic velocity	20% in both sexes
[144]	134 type 2 diabetes patients	↓ mean peak systolic early + diastolic velocity, ↓ mean isovolumic relaxation time, ↑ systolic + diastolic synchronicity	20% in both sexes

**Abbreviations:** DCM, diabetic cardiomyopathy; DM, diabetes mellitus; IGT, impaired glucose tolerance; LV, left ventricular; HTN, hypertension; TEI, total ejection isovolumic; MetS, metabolic syndrome; IB, integrated backscatter.

to a control group or to 1 of the 3 active treatment groups, ie, diet only, exercise only, or diet plus exercise. The cumulative incidence of DCM at 6 years was 67.7% in the control group compared with 43.85% in the diet group, 41.1% in the exercise group, and 46% in the diet plus exercise group. Each of the active intervention groups differed significantly from the control group ( $P < 0.05$ ). In a proportional hazards analysis comparing the 3 intervention groups to the control group, there was a reduction in the cardiovascular risk of 33% in the diet group ( $P < 0.03$ ), 47% in the exercise group ( $P < 0.0005$ ), and 38% in the diet plus exercise group ( $P < 0.005$ ). In conclusion, lifestyle changes with diet and/or exercise interventions led to a significant decrease in the incidence of DCM over a 6-year period among subjects with type 2 diabetes.<sup>145</sup>

Another randomized, blinded study with a mean duration of 3.2 years evaluated the feasibility and effects of a program of lifestyle changes designed to prevent or delay the onset of type 2 diabetes in 523 middle-aged, overweight

(BMI ~31.3 kg/m<sup>2</sup>) subjects with impaired glucose tolerance and the incidence of DCM in patients with type 2 diabetes.<sup>146</sup> The intervention group consisted of individualized counseling aimed at reducing weight and total fat intake and increasing fiber intake and physical activity (at least 30 min per day). During the trial, the risk of diabetes was reduced by 58% in the intervention group and was directly associated with changes in lifestyle. The changes in lifestyle also reduced (by 56% in both men and women) the magnitude of DCM incidence.<sup>147</sup>

Cigarette smoking is an obvious and important modifiable risk factor for cardiovascular disease. Smoking cessation confers immediate and lasting benefits that are likely to be even greater in people with diabetes, whose vascular risk is further increased by smoking. In the Multiple Risk Factor Intervention Study (MRFIT), the absolute risk of cardiovascular death over 12 years was much higher for diabetes subjects compared with the nondiabetes participants

and was significantly associated with reported number of cigarettes/day ( $P < 0.0001$ ). Together with dyslipidemia and hypertension, cigarette smoking was a dominant predictor of cardiovascular morbidity (increased risk for DCM by 53% in both sexes) and cardiovascular mortality (overall 3 times higher risk of death from heart failure).<sup>103,148</sup>

## Optimizing glycemic control

This is an important treatment aim in the management of DCM. A prospective cohort study analyzed the relative risk of macrovascular disease in patients with newly diagnosed type 2 diabetes and determined whether an intensive approach to dietary management, besides satisfactory glycemic control, would ameliorate the long-term cardiovascular risk and reduce the incidence of DCM and cardiovascular mortality. The study compared dietary management alone to oral hypoglycemic therapy (tolbutamide 500 mg or metformin twice a day) with continued diet and finally insulin regimen. At the end of the 10-year follow-up period, the survival rate was 75%, whereas 26% of the patients suffered myocardial infarction, of which 41% was fatal. The analysis of baseline data showed a relative risk equal to 1.04 for myocardial infarction for each 1 mmol/L increase in fasting plasma glucose. The risk of myocardial infarction while on insulin or oral treatment was not significantly elevated relative to dietary treatment. The study concluded that fasting plasma glucose is a significantly independent predictor of diabetic macrovascular disease, and the type of antidiabetic treatment does not prevent long-term cardiovascular disease.<sup>149</sup>

The epidemiological analysis of a prospective, multicenter, population-based study of patients with newly diagnosed type 2 diabetes demonstrated that the incidence of myocardial infarction was 15.2% and of these 19.2% died. The results showed that good glycemic control was associated with lower risk not only for myocardial infarction (15.2% vs 42%) but also for DCM (15% vs 32%). Good glycemic control was associated with a lower incidence of DCM (27% vs 9%), whereas postprandial blood glucose levels were among the independent predictors for cardiovascular morbidity and mortality.<sup>150,151</sup> The UKPDS evaluated the relationship between exposure to glycemia over time and the development of DCM in patients with type 2 diabetes. For each 1% reduction in mean HbA<sub>1c</sub>, there was a 14% associated decrease in risk for myocardial infarction and a 16% decrease in risk for heart failure.<sup>152</sup>

## Management of dyslipidemia

A double-blind, randomized, placebo-controlled, multicenter clinical trial assessed the effect of cholesterol lowering with

simvastatin on mortality and the risk of coronary heart disease in patients with diabetes and DCM. Treatment of dyslipidemia significantly decreased the risk of coronary heart disease (recurrent myocardial infarction) by 55% ( $P = 0.002$ ) in subjects with type 2 diabetes. Since in diabetes subjects with DCM the case fatality is very high, aggressive lipid lowering should be extended to diabetes subjects who have not yet experienced a clinical event (primary and secondary prevention).<sup>153</sup>

Another multicenter, randomized, double-blind, placebo-controlled study determined if treatment with gemfibrozil would reduce the incidence of major cardiovascular events and outcomes in patients with type 2 diabetes. DCM was reduced by 22% with gemfibrozil treatment, and major cardiovascular events were reduced by 24%. For every 5 mg/dL increase in HDL cholesterol, there was an 11% reduction in cardiovascular events.<sup>154</sup> The effect of lipid-lowering treatment at various levels of glucose tolerance or hyperinsulinemia was also evaluated by the same group, and the association between diabetes status, glucose–insulin levels and cardiovascular risk was examined. In patients with diabetes, a fasting plasma insulin level  $\geq 271$  pmol/L was associated with a 31% increased risk of cardiovascular events. Gemfibrozil was effective in patients with diabetes, and the reduction in DCM was 53%, whereas in cardiovascular mortality, it was 41%.<sup>155–157</sup>

## Hypertension management and renoprotection

A randomized, double-blind, active-controlled clinical trial reached to determine whether the combined incidence of fatal coronary heart disease and nonfatal myocardial infarction differs between diuretic treatment (chlorthalidone) and 3 alternative therapies: calcium channel blockers (amlodipine), ACE inhibitors (lisinopril), and  $\alpha$ -blockers (doxazosin). The incidence of DCM was higher in the group under therapy with  $\alpha$ -blockers compared with diuretics (relative risk equal to 1.25 at a 4-year rate). No significant differences were observed between calcium channel blockers, ACE inhibitors, and diuretics for the primary outcome or for all-cause mortality. Amlodipine had a higher 6-year rate of heart failure (10.2% vs the diuretic group) and of hospitalized or fatal heart failure (8.4%). Lisinopril was associated with a 10% higher risk of DCM and a 19% higher risk for heart failure. Five-year systolic blood pressure was significantly higher in the amlodipine group (0.8 mm Hg;  $P = 0.03$ ), and lisinopril (2 mm Hg;  $P < 0.001$ ) groups, compared with chlorthalidone. Thus, thiazide-type diuretics

should be considered first for antihypertensive treatment and for patients who cannot be treated with diuretics; calcium channel blockers and ACE inhibitors could be considered as alternative choices.<sup>158</sup>

A double-blind, randomized, 2 × 2 factorial study, the Heart Outcomes Prevention Evaluation (HOPE) study, compared an ACE inhibitor, ie, ramipril, vs placebo in preventing death from cardiovascular causes, myocardial infarction, or all-cause death. The study concluded that ramipril significantly reduced the rates of death (6.1% compared with 8.1% in the placebo group), myocardial infarction (9.9% vs 12.3%), and all-cause mortality (10.4% vs 12.2%). Moreover, ramipril therapy significantly decreased the rate of heart failure (9% vs 11.5% in the placebo group) and of DCM (6.4% vs 7.6%;  $P = 0.03$ ). Ramipril achieved a significant reduction in the new cases with diabetes in the high-risk population included in the study, with unknown myocardial dysfunction (low ejection fraction) or heart failure.<sup>159</sup>

The association between major cardiovascular events and the achievement of different blood pressure targets during antihypertensive therapy, as well as the addition of low doses of acetylsalicylic acid was assessed in another randomized trial. Felodipine (5 mg/d) was given as baseline therapy, and other agents were added according to a 5-step regimen. The lowest incidence of DCM and major cardiovascular morbidity and mortality occurred in the blood pressure target group of  $\leq 135/80$  mm Hg. DCM was reduced by 51%, and the addition of acetylsalicylic acid further achieved a 15% reduction in major cardiovascular morbidity and a 36% reduction in myocardial infarction. The study demonstrated that active lowering of blood pressure is particularly beneficial in patients with diabetes and that addition of a small dose of acetylsalicylic acid, provided that blood pressure is well controlled and the risk of gastrointestinal and nasal bleeding is carefully assessed, further reduces the risk of acute myocardial infarction.<sup>160</sup>

A double-masked, randomized, parallel-controlled group trial determined the effectiveness of losartan, a selective angiotensin II type 1 (AT1) receptor antagonist in comparison with the  $\beta$ -blocker atenolol in reducing cardiovascular morbidity and mortality in diabetes patients with hypertension and LV hypertrophy. Losartan was more effective than atenolol in reducing cardiovascular morbidity and mortality (76% reduction of the relative risk of a primary cardiovascular end point). The greater cardiovascular protection of losartan was attributed mainly to the result of a more pronounced protection against the detrimental effects of angiotensin II.<sup>161</sup>

A randomized controlled trial, further determined the effectiveness of tight blood pressure control ( $< 150/85$  mm Hg) with the use of an ACE inhibitor (captopril) or a  $\beta$ -blocker (atenolol) as main treatment in the reduction of cardiovascular morbidity and mortality. Reduction in cardiovascular risk by 24% in all end points related to diabetes was achieved with tight blood pressure control (32% in deaths). In addition, there was a 56% reduction in the risk of heart failure.<sup>162</sup>

Microalbuminuria heralds a further increase in risk of myocardial infarction and necessitates even stricter blood pressure control. A randomized control trial determined that blood pressure lowering with captopril and atenolol is equally effective and safe in reducing the risk of fatal and nonfatal macrovascular and microvascular complications in patients with type 2 diabetes.<sup>163</sup> ACE inhibitors largely remain in the antihypertensive class of choice, as their use delays the progression of nephropathy.<sup>164</sup>

## Medical management of cardiovascular disease in diabetes

Heart failure is also conventionally managed with diuretics and ACE inhibitors. Certain  $\beta$ -blockers, such as carvedilol, are among the drugs of choice for patients with diabetes, due to the fact that it has a beneficial effect on insulin resistance and a neutral activity on the lipid profile of patients with diabetes.<sup>165,166</sup> The results of the intervention studies for the prevention of DCM are summarized in Table 2.

## Struggling toward additional knowledge Targeting the pathophysiological substrate: new experimental therapies, regimens, and remedies

Recently, direct correlations between apelin plasma levels and the structural and functional alterations, ie, LV hypertrophy and pressure overload, were demonstrated in humans and diabetic rats with DCM. A parallel study was conducted in streptozotocin-induced diabetic rats, where pressure overload was established by suprarenal aortic banding, as well as in patients with diabetes, where during surgery for aortic and mitral stenosis, LV function and structure were evaluated by 2DE and LV endomyocardial biopsies were procured. In both situations, the myocardial expression of apelin was significantly downregulated by pressure overload and apelin plasma levels were accordingly elevated. Since activation of the apelinergic system has a direct positive inotropic and vasodilatation effect, it was concluded that elevation in apelin

**Table 2** Major studies on treatment strategies of diabetic cardiomyopathy

Reference	Type of diabetes	Intervention	Purpose	Follow-up period	Treatment regimen	Results
[145]	2	Diet/exercise	↓ incidence of DCM	6 y	Control (n = 195) vs exercise (n = 211)	33% ↓ in the diet group 47% ↓ in the exercise group 38% ↓ in the diet + exercise
[146,147]	2/IGT	Behavioral diet + physical therapy	↓ onset of diabetes ↓ DCM incidence	3.2 y	Individualized counseling vs general oral and written information about diet/exercise	58% ↓ in the intervention group of diabetes 56% ↓ in the intervention group of DCM
[149]	2, newly diagnosed	Prolonged dietary management	↓ DCM incidence ↓ of cardiovascular mortality	10 y	Diet alone (n = 219) vs diet + tolbutamide 500 mg/metformin twice a day (n = 140) vs insulin (n = 73)	1.04 RR for MI per ↑ 1 mmol/L in fasting plasma glucose, no difference between treatments for the risk of MI
[150]	2, newly diagnosed	Intensified health education	↓ MI incidence ↓ all-cause mortality	11 y	a. Usual care (n = 378) vs b. intensified health education (n = 334) vs b + 1.6 clofibrilic acid/day (n = 332)	15.2% patients suffered from MI and 19.2% died, postprandial glucose levels were independent risk factors for CVD death
[152]	2	none	Evaluation of hyperglycemia exposure to the incidence of DCM	10 y	Not applicable	Each 1% ↓ in HbA <sub>1c</sub> was associated with: 14% ↓ in risk for MI 16% ↓ in risk for HF 55% ↓ in CVD risk
[153]	2	Simvastatin 20 to 40 mg	Prevention of recurrent CVD in DCM	5.4 y	Placebo vs simvastatin 20 to 40 mg per day	
[154]	2	Gemfibrozil 1,200 mg/day	Changes in plasma lipids could reduce major CVD events	7 y	Placebo (n = 1.267) vs gemfibrozil 1,200 mg/day (n = 1.264)	22% ↓ of CVD events for every 5 mg/dL ↑ in HDL-C, there was an 11% ↓ in CVD events
[155]	2	Gemfibrozil 1,200 mg/day	Efficacy of gemfibrozil in varying glucose levels association between hyperglycemia and CVD risk	7 y	Placebo (n = 1.267) vs gemfibrozil 1,200 mg/day (n = 1.264)	Fasting insulin ≥ 271 pmol/L was associated with: 31% ↑ CVD risk 41% ↓ in CVD death
[158]	2	Diuretic or Ca-blocker or ACE	Differences in CVD risk between antihypertensive regiments	4.9 y	Diuretic (chlorthalidone 12.5 to 25 md/d, n = 15.255) or Ca-blocker (amlodipine 2.5 to 10 mg/d, n = 9.048), or ACE inhibitor (lisinopril 10 to 40 mg/d, n = 9.054)	10.2% ↑ risk of HF with amlodipine 19% ↑ risk of HF with lisinopril 33.3% ↑ risk of DCM with lisinopril, better blood pressure control with chlorthalidone
[159]	2	Ramipril 10 mg/day	Prevention death from CVD, MI, all-cause mortality, HF, DCM, development of diabetes	5 y	Placebo (n = 4.652) vs ramipril (n = 4.645)	6.1% ↓ of CVD death 9.9% ↓ of MI 10.4% ↓ of all-cause death 9% ↓ of HF 6.4% ↓ of DCM 3.6% ↓ in new diabetes
[160]	2	Felodipine 5 mg/day	Achievement of blood pressure targets with the addition of ASA and association to DCM and CVD risk	3.8 y	Felodipine 5 mg/d + ASA vs felodipine 5 mg/d + placebo	51% ↓ of CVD risk in target ≤ 135/80 mm Hg + 15% ↓ of CVD risk with ASA and 36% ↓ in MI

(Continued)

**Table 2** (Continued)

Reference	Type of diabetes	Intervention	Purpose	Follow-up period	Treatment regimen	Results
[161]	2	Losartan 50 to 100 mg/d	↓ of CVD risk with losartan vs atenolol	4.7 y	Losartan 50–100 mg/d (n = 586) vs atenolol 50–100 mg/d (n = 609)	76% ↓ of relative CVD risk
[162]	2	Blood pressure control < 150/80 mm Hg	↓ of CVD risk	8.4 y	Captopril (50–100 mg/d, n = 400) vs atenolol (50–100 mg/d, n = 358)	24% ↓ of CVD risk 32% ↓ of death 56% ↓ of HF
[164]	2	Irbesartan 300 mg/d vs amlodipine 10 mg/d	↓ of blood pressure provides protection against progression of nephropathy	2.6 y	Irbesartan (300 mg/d, n = 579) vs amlodipine (10 mg/d, n = 567) vs placebo	With irbesartan: 37% ↓ risk of doubling serum creatinine 23% ↓ risk of end-stage renal disease 23% ↓ risk of HF
[166]	2	Clopidogrel 300 mg/d bolus, followed by clopidogrel 75 mg/d for 3–12 mo	↓ of CVD mortality	1 y	Clopidogrel 300 mg/d bolus, followed by clopidogrel 75 mg/d for 3–12 mo vs placebo	15% ↓ of MI rate

**Abbreviations:** DCM, diabetic cardiomyopathy; IGT, impaired glucose tolerance; RR, relative risk; MI, myocardial infarction; CVD, cardiovascular disease death; HF, heart failure; HDL-C, high density lipoprotein-cholesterol levels; Ca-blocker, calcium channel blocker; ACE, angiotensin-converting-enzyme; ASA, acetylsalicylic acid.

plasma levels may represent a compensatory mechanism to maintain inotropism and cardiac output during pressure overload conditions, such as DCM.<sup>167</sup>

The kinins are vasoactive peptides and part of the kallikrein–kinin system (KKS). Recent studies have demonstrated that they are involved in different aspects of remodeling, inflammation, and angiogenesis. It is increasingly recognized that the KKS is involved in the inflammatory processes of the heart. Evidence shows that the KKS has beneficial effects in myocardial diseases by protecting from inflammation, fibrosis, and apoptosis. KKS also shows a proinflammatory character by increasing the production of cytokines and stimulating the migration of immune cells. Novel important actions of the KKS contribute to neovascularization and recruitment of endothelial progenitor cells in ischemic areas and endothelial dysfunction. All these evidence support that the KKS could constitute a potential therapeutic target in the treatment of myocardial ischemia and DCM.<sup>168</sup>

As previously discussed,<sup>47</sup> a significant role in the myocardial dysfunction of DCM is supported by the reduction of the sarcoplasmic calcium ATPase myocardial expression (SERCA2). Resveratrol, a potent activator of the cardiac function and the SERCA2 in type 1 diabetes were recently administered to adult male streptozotocin-induced diabetic mice, where the induced diabetes produced a progressive decline in cardiac function associated with markedly reduced SERCA2 and increased collagen deposition. Resveratrol treatment to these mice had a tremendous beneficial effect both in terms of improving SERCA2 expression and cardiac function.

The data demonstrate that in DCM, where the expression of SERCA2 is reduced, resveratrol enhances the expression of the SERCA2 and improves cardiac function.<sup>169</sup>

Cardiac fibrosis and protein O-glycosylation are elevated in DCM.<sup>22,23</sup> One in vitro study in rat cardiac fibroblasts recently demonstrated that long-term glucose load significantly increases collagen expression. Treatment with glucosamine not only induced the collagen expression but also increased the O-glycosylated protein. These results suggest that O-glycosylation of protein modifies collagen expression and, therefore, contributes to DCM.<sup>170</sup> ROSs play an important role in the development of DCM.<sup>42,43</sup> Matrix metalloproteinase 2 (MMP-2) is activated by ROS and contributes to the acute loss of myocardial contractile function by targeting and cleaving susceptible proteins including troponin I and  $\alpha$ -actinin. Using the streptozotocin-induced diabetic rat model, one study evaluated the 4-week administration effect on heart function of a daily in vivo administration of sodium selenate (0.3 mg/kg) or a pure  $\omega$ -3 fish oil with antioxidant vitamin E ( $\omega$ -3E, 50 mg/kg). Both treatments prevented the diabetes-induced functional changes; however, the improvement in myocardial function was greater with sodium selenate compared with that of the omega-3E. Moreover, these treatments reduced the diabetes-induced increase in myocardial oxidized protein sulfhydryl and nitrite concentrations. The diabetes-induced changes in myocardial levels of MMP-2 were associated with a significant reduction in troponin I and  $\alpha$ -actinin protein levels in both treatment groups. These results suggest that diabetes-induced alterations in MMP-2 contribute to myocardial contractile dysfunction by targeting

troponin I and  $\alpha$ -actinin and that sodium selenate or omega-3E could have therapeutic benefits in DCM.<sup>171</sup>

Another study also aimed at the suppression of mitochondrial oxidative stress and mitochondrion-dependent myocardial apoptosis with the administration of antioxidant  $\alpha$ -lipoic acid ( $\alpha$ -LA) to prevent evolution of DCM. In a streptozotocin-induced diabetic rat model,  $\alpha$ -LA was administered (100 mg/kg intraperitoneally per day) for 12 weeks. Antioxidant  $\alpha$ -LA effectively attenuated mitochondrion-dependent cardiac apoptosis and exerted a protective role against the development of DCM. The ability of  $\alpha$ -LA to suppress mitochondrial oxidative damage was concomitant with an enhancement of manganese superoxide dismutase activity in the myocardial mitochondria and an increase in the glutathione content of myocardial mitochondria.<sup>172</sup>

The diabetic heart is resistant to ischemic preconditioning because of diabetes-associated impairment of phosphatidylinositol 3-kinase (PI3K)-Akt signaling. One study examined the hypothesis that phosphorylation of Janus kinase 2 (Jak2) upstream of PI3K is impaired in diabetic hearts by an AT1 receptor-mediated mechanism. Thus, in a type 2 diabetic rat model, myocardial infarct was produced. Erythropoietin (EPO) administration activated the Jak2-mediated signaling and limited the infarct size in experimental rats. Where EPO failed to induce infarct size limitation, blockade of the AT1 receptor by valsartan or losartan treatment for 2 weeks restored the myocardial response to EPO. Furthermore, treatment with valsartan normalized the calcineurin activity in diabetic rats. These results suggest that the diabetic heart is refractory to protection by Jak2-activating ligands because of AT1 receptor-mediated upregulation of calcineurin activity.<sup>173</sup>

The  $\beta$  isoform of protein kinase C (PKC- $\beta$ ) is a target implicated in diabetic complications. To investigate the influence of breviscapine on the cardiac structure and function in rats with DCM, as well as the expression of PKC and  $Ca^{2+}$  cycling proteins, type 2 diabetic rats were treated with breviscapine for 6 weeks, and invasive cardiac function and echocardiographic parameters were measured, while heart tissue was obtained for electron microscope study. Treatment with breviscapine reversed the cardiac dysfunction and structure changes in rats with DCM, decreased the expression of PKC, and increased the expression of calcium handling regulators, ie, protein phosphatase inhibitor-1, phospholamban, and SERCA2. This study showed that breviscapine has a protective effect on DCM, which is dose related.<sup>174</sup> Breviscapine also prevented cardiac hypertrophy in diabetic rats by inhibiting the expression of PKC, which may have a

protective effect in the pathogenesis of DCM via the PKC/NF- $\kappa$ B/c-fos signal transduction pathway.<sup>175</sup>

Using a hemodynamically validated rodent model of diabetic diastolic heart failure, the (mRen-2)27 transgenic rat another study further determined the selective inhibition of PKC- $\beta$ . Preservation of cardiac function and reduction of structural injury were evaluated. Diabetic rats were randomized to receive either vehicle or the PKC- $\beta$  inhibitor, ruboxistaurin (20 mg/kg/day) and followed for 6 weeks. Compared with untreated animals, ruboxistaurin-treated diabetic rats demonstrated preserved systolic and diastolic function. Collagen deposition and cardiomyocyte hypertrophy were both reduced in diabetic animals treated with ruboxistaurin as was phosphorylated-Smad2, an index of transforming growth factor  $\beta$  (TGF- $\beta$ ) activity. PKC- $\beta$  inhibition attenuated diastolic dysfunction, myocyte hypertrophy, and collagen deposition and preserved cardiac contractility. PKC- $\beta$  inhibition may represent a novel therapeutic strategy for the prevention of diabetes-associated cardiac dysfunction.<sup>176</sup>

Studies have shown that caffeic and ellagic acid, 2 phenolic acids naturally occurring in many plant foods, can provide triglyceride-lowering, anticoagulatory, antioxidative, and anti-inflammatory protection in cardiac tissue of diabetic mice. Thus, the supplement of these agents might be helpful for the prevention or attenuation of DCM.<sup>177</sup>

Total aralosides of *Aralia elata* (Miq) Seem (TASAES) from the Chinese traditional herb Longya *Aralia chinensis* L. has been demonstrated to improve cardiac function. A recent study determined the protective effects of TASAES on DCM in streptozotocin-induced diabetic rats. Diabetic rats were treated with TASAES for 8 weeks. Cardiac function was evaluated by in situ hemodynamic measurements. TASAES showed a significant protection against diabetes-induced cardiac dysfunction and enhanced the amplitude of  $Ca^{2+}$  channel currents. Moreover, histological staining indicated a significant inhibition of diabetes-caused pathological changes and upregulation of profibrotic factor, and connective tissue growth factor, and expression. The results suggest that TASAES prevents diabetes-induced cardiac dysfunction and pathological damage.<sup>178</sup>

The effects of *Ginkgo biloba* extract (EGb 761), a radical scavenger, against diabetes-induced myocardial interstitium and microvasculature damage and against additional ischemia or reperfusion injury in spontaneously diabetic BioBreeding/Ottawa Karlsburg (BB/OK) rats modeling diabetic cardiac infarction were also investigated as an alternative antioxidative therapy. Pretreatment of diabetic myocardium with EGb resulted in an improvement of impaired endothe-

lial-dependent vasodilatation in diabetes and additional ischemia or reperfusion, diminished mast cell and substance P accumulation, and better preserved myocardial ultrastructure compared with unprotected myocardium. EGb may act as a potent therapeutic adjuvant in patients with diabetes with respect to ischemic myocardial injury and may contribute to preventing late complications in DCM.<sup>179</sup> Another study, also demonstrated EGb as a promising adjuvant therapeutic drug in patients with diabetes with respect to ischemic myocardium injury. It concluded that it may contribute to the prevention of late diabetic complications in DCM.<sup>180</sup>

Natural medicine for the treatment of DCM was further recognized by the demonstration of grape seed proanthocyanidin extracts (GSPEs) as therapeutic agents against DCM in streptozotocin-induced diabetic rats. GSPEs decreased AGEs and ameliorated glycation-associated cardiac damage.<sup>181</sup>

Recent studies in mice experimental models with acute ischemic injury revealed that EPO has numerous tissue-protective effects in the heart, brain, and kidneys. One study explored the tissue-protective properties of chronic EPO treatment in an experimental model of the db/db mouse with diabetic heart injury. Continuous erythropoietin receptor activator (CERA)-treated mice had a significant reduction in TGF- $\beta$ 1 and collagen I expression in cardiac tissue. Atrial natriuretic peptide expression was increased in CERA-treated mice. Chronic treatment with CERA protects cardiac tissue in diabetic animals by inhibiting molecular pathways of cardiac fibrosis, and the effects are dose dependent.<sup>182</sup>

## Cell-based myocardial regenerative therapy

Cell-based myocardial regenerative therapy can be potentially applied in the treatment of DCM in order to limit the consequences of decreased contractile function and compliance of damaged ventricles, owing to ischemic and nonischemic myocardial areas. A variety of myogenic and angiogenic cell types have been proposed, such as skeletal myoblasts, mononuclear and mesenchymal bone marrow cells, circulating blood-derived progenitors, adipose-derived stromal cells, induced pluripotent stem cells, umbilical cord cells, endometrial mesenchymal stem cells, adult testis pluripotent stem cells, and embryonic cells. It is important to note that stem cells are not an alternative to heart transplantation; selected patients should be in an early stage of heart failure, as the goal of this regenerative approach is to avoid or delay organ transplantation. Since the cell niche provides crucial support needed for stem cell maintenance, the most

interesting and realistic perspectives include the association of intramyocardial cell transplantation with tissue-engineered scaffolds and multisite cardiac pacing in order to transform a passive regenerative approach into a “dynamic cellular support,” a promising method for the creation of “bioartificial myocardium”.<sup>183</sup>

## Conclusion

DCM is not uncommon and is associated with increased morbidity and mortality in patients with diabetes. Metabolic pathway deregulation in diabetes adversely affects the cardiac myocytes, as well as every cellular element within the vascular walls. Other pathogenetic mechanisms involved in decreasing myocardial contractility in DCM are impaired calcium homeostasis, renin–angiotensin system upregulation, increased oxidative stress, altered substrate metabolism, and mitochondrial dysfunction.<sup>184</sup> Continued research has provided novel insights into underlying molecular and pathophysiological mechanisms that increase the vulnerability of the diabetic heart to failure.<sup>185</sup> The choice of antidiabetic medication may influence the cardiovascular outcome.<sup>186,187</sup> However, intensive treatment of the gamut of metabolic abnormalities associated with diabetes beyond hyperglycemia reduces the rates of DCM, myocardial infarction, and associated cardiovascular death. As this high-risk population increases, elucidation of the mechanisms responsible for DCM will further motivate the generation of novel therapies tailored to decrease the cardiovascular morbidity and mortality in diabetes. Strategies to encourage the aggressive use of targeted medical therapies will further reduce the magnified rates of the diabetic heart failure burden.

## Disclosure

The authors report no conflicts of interest in this work.

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