REVIEW

Diabetic cardiomyopathy: Myth or reality?

Cardiomyopathie diabétique: mythe ou réalité?

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Summary Diabetes mellitus has reached an epidemic level worldwide. Cardiovascular diseases are the primary cause of death in diabetic patients, not only because of coronary artery disease and associated hypertension but also because of a direct adverse effect of diabetes on the heart, independent of other potential aetiological factors. However, the existence of this ‘diabetic cardiomyopathy’ remains controversial. We aimed to review current evidence for the existence of diabetic cardiomyopathy, focusing particularly on the clinical setting.

Résumé Le diabète a atteint un niveau épidémique sur le plan mondial. Les pathologies cardiovasculaires représentent la première cause de décès chez les patients atteints de diabète non seulement du fait des cardiopathies ischémiques et de l’hypertension artérielle associées au diabète mais également du fait d’un effet délétère du diabète lui-même sur le plan cardiovasculaire indépendamment de tout autre facteur étiologique potentiel. Cependant, l’existence de cette « cardiomyopathie diabétique » reste controversée. Le but de cette revue de la littérature est de discuter des preuves de l’existence d’une cardiomyopathie diabétique en s’intéressant principalement au champ clinique.

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Abbreviations: BMI, body mass index; CI, confidence interval; CITP, carboxy-terminal telopeptide of collagen type I; DCM, diabetic cardiomyopathy; LV, left ventricular; MMP, matrix metalloproteinase; PICP, carboxy-terminal propeptide of procollagen type I; STI, speckle tracking imaging; TDI, tissue Doppler imaging; TIMP, tissue inhibitors of matrix metalloproteinase.
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**Background**

A tsunami of obesity has been recently described, with 1.46 billion overweight adults (BMI ≥ 25 kg/m²) in 2008, including 500 million who were obese (BMI ≥ 30 kg/m²) [1]. Consequently, diabetes mellitus has reached an epicemic level worldwide, with a prevalence of 4% in 1995 and an anticipated prevalence of 5.4% in 2025, corresponding to 300 million adults with diabetes worldwide [2]. Cardiovascular diseases represent the primary cause of death in this population because of coronary artery disease [3] or associated hypertension but also because of a direct adverse effect of diabetes mellitus on the heart, called DCM. Diabetes mellitus is a complex metabolic disorder that includes insulin resistance (in type 2), often associated with hypertension and obesity [4]. All those conditions are associated with a high risk of coronary artery disease but may also exert a direct negative effect on the myocardium. Among them, the specific negative effect of diabetes mellitus on the heart, leading to DCM, has been extensively investigated in the last three decades. Controversies exist regarding the existence of a specific DCM, as this concept has mainly emerged from experimental models [5]. In this review, we aimed to discuss the current evidence for the existence of DCM, focusing particularly on the clinical setting.

**Definition of diabetic cardiomyopathy (DCM)**

DCM was first described 40 years ago, based on post-mortem observations in four diabetic patients with heart failure but no coronary artery disease or other aetiological conditions explaining heart failure [6]. The authors observed LV hypertrophy associated with myocardial fibrosis in those patients and introduced for the first time the concept of DCM [6]. Five years later, Regan et al. [7] confirmed those results and described cases of heart failure in familial diabetes without coronary artery disease, hypertension or obesity. A higher myocardial collagen and lipid content was also reported in those cases compared with control subjects [7].

Since those initial studies, DCM has been defined as the existence of LV dysfunction in diabetic patients without coronary artery disease, hypertension or other potential aetiological condition.

**Experimental evidence**

Numerous experimental studies, mainly based on rodent models, have demonstrated a direct negative effect of diabetes mellitus on the myocardium [8,9]. Pathophysiological mechanisms include metabolic alterations with impaired calcium homeostasis, alteration of substrate utilization (increase in lipid use and decrease in glucose oxidation), lipotoxicity, glucotoxicity with intervention of advanced glycation end products, mitochondrial dysfunction, increase in oxidative stress, renin-angiotensin-aldosterone system activation and cardiac dyssynchrony. All these mechanisms lead to an increase in myocardial cellular death (necrosis and apoptosis) and to myocardial fibrosis, with the consequent development of myocardial dysfunction and overt heart failure (Fig. 1) [8,9].

**Epidemiological evidence**

In the clinical setting, the most convincing evidence for the existence of DCM comes from large epidemiological studies. Two years after the study of Rubler et al. [6], the Framingham Heart Study investigators demonstrated that diabetes mellitus was an independent risk factor for heart failure [10]. Risk of heart failure was 2.4-fold and 5-fold higher in diabetic men and women, respectively, than in non-diabetic subjects. The increased incidence of heart failure in diabetic patients persisted even after adjustment for age, hypertension, obesity, coronary artery disease or dyslipidaemia [10].

Diabetes mellitus as an independent risk factor for heart failure has been confirmed in numerous epidemiological studies [11–17]. In a prospective study including 2700 elderly subjects (mean age 81 ± 9 years), the incidence of heart failure during a 43-month follow-up was 1.3-fold higher in diabetes mellitus than in euglycaemic subjects after adjustment for age, hypertension, coronary artery disease and sex [11]. The Cardiovascular Health Study, including 5888 subjects aged more than 65 years with a mean delay of 5.5 years follow-up, reported an incidence rate for heart failure of 19.3/1000 person-years, with a substantially higher incidence (approximately 2-fold) associated with diabetes mellitus [15]. In a large case-control study, Bertoni et al. [12] tested the hypothesis that diabetes mellitus was independently associated with idiopathic cardiomyopathy. After adjusting for age, sex, race and hypertension, diabetes
mellitus was significantly associated with idiopathic cardiomyopathy (relative odds 1.58, 95% CI 1.55–1.62). Those results were confirmed in a second case-control study [13]. In the French EPICAL Study, prevalence of diabetes mellitus among patients with non-ischaemic advanced heart failure was 19.7% [17]. In the Reykjavik Study, Thrainsdottir et al. [16] explored the associations between heart failure and abnormal glucose regulation (impaired glucose tolerance or impaired fasting glucose) or type 2 diabetes mellitus in a population-based cohort of 19,381 participants. The odds ratio was 2.8 (95% CI 2.2–3.6) for the association between type 2 diabetes mellitus and heart failure and 1.7 (95% CI 1.4–2.1) for the association between abnormal glucose regulation and heart failure.

Finally, the Strong Heart Study recently confirmed diabetes mellitus as an independent risk factor of heart failure [14]. In a population-based cohort of 1204 subjects, the authors showed a 1.5-fold higher risk of heart failure in patients with diabetes mellitus after adjustment for multiple cofactors (age, sex, obesity, central fat distribution, antihypertensive medications, atrial fibrillation, urinary albumin/creatinine ratio, plasma cholesterol, HbA1c, smoking habit, alcohol use, educational level and physical activity). Interestingly, for the first time, intercurrent myocardial infarction was censored in this analysis [14].

Noninvasive evidence for adverse effects of diabetes mellitus on the heart (left ventricular structure, remodelling and function)

Noninvasive evidence for structural myocardial abnormalities associated with diabetes

Myocardial fibrosis

Myocardial fibrosis, as initially described by Rubler et al. [6] and confirmed in both histological studies in humans [7,18,19] and experimental studies [20], is a major consequence of the adverse effects of diabetes mellitus on the heart [8]. Backscatter is an ultrasound tissue characterization technique based on the measurement of myocardial tissue echoreactivity, which is related to myocardial collagen content [21]. Di Bello et al. [22] showed an increase in myocardial echodensity as assessed by the integrated backscatter index in 26 insulin-dependent diabetic normotensive patients compared with 17 age- and sex-matched control subjects. Fang et al. [23] confirmed these results using calibrated integrated backscatter in a larger study.

Biomarkers of collagen synthesis (PICP; PINP, amino-terminal propeptide of procollagen type I; PIIINP, carboxy-terminal propeptide of procollagen type III; PIIINP, amino-terminal propeptide of procollagen type III) or collagen degradation (CITP) have been shown to be of clinical interest in detecting myocardial fibrosis [24]. In addition, markers of extracellular matrix turnover (such as MMP) and their inhibitors (TIMP, tissue inhibitors of MMP) might also be useful [24]. However, few studies have used these biomarkers in diabetic patients. An increase in CITP was recently described in type 2 diabetic patients compared with control subjects and was correlated with diastolic function (mitral A duration minus pulmonary vein atrial reversal velocity duration) [25]. MMP-7 has also been shown to be associated with diastolic dysfunction with microvascular complications (nephropathy) [26]. Patients with diastolic dysfunction demonstrated an increase in MMP-9 and a decrease in TIMP-1/MMP-9 [26]. Finally, in a small group of diabetic patients, correlation was found between PICP and LV systolic variables (fractional shortening and midwall fractional shortening) [27].

Myocardial steatosis

An increase in myocardial lipid content (myocardial steatosis) has been demonstrated in diabetic patients using 1H-magnetic resonance spectroscopy. McGavock et al. [28] showed an increase in myocardial triglyceride content in glucose intolerant patients and in patients with type 2 diabetes mellitus compared with controls. Myocardial triglyceride content was associated with diastolic function variables (E/A ratio and E wave deceleration time) [29]. In a group of 42 men with type 2 diabetes mellitus, patients with a high myocardial triglyceride content (superior to the median of the population) presented a decrease in systolic strain and strain rate whereas LV ejection fraction was similar in the two groups [30].

These structural abnormalities are associated with morphological and functional abnormalities

Concentric remodelling and left ventricular hypertrophy

Concentric remodelling is defined as an increase in relative wall thickness ([2 × posterior wall thickness]/end-diastolic diameter) with normal LV mass index values, whereas LV hypertrophy is defined as abnormal LV mass index values [31]. Concentric remodelling and LV hypertrophy, known to be of adverse prognostic value [32], are the most frequently described morphological abnormalities associated with diabetes mellitus [33–37]. In the Framingham Heart Study, Galderisi et al. [35] showed an increase in LV mass and wall thickness independently associated with diabetes mellitus, but in multivariable analysis, statistical significance was reached only in women. In the Cardiovascular Health Study, an increase in LV mass was independently associated with diabetes mellitus even after adjustment for body weight, blood pressure, heart rate and prevalent coronary or cerebrovascular disease [36]. However, in contrast to previous findings, this association was significant in both men and women [36]. The Strong Heart Study confirmed these results in a large cohort of American Indians (1810 participants with diabetes mellitus and 944 glucose-tolerant subjects) [33]. In this population, increases in wall thickness and LV mass were associated with a slight decrease in LV fractional shortening and midwall fractional shortening in diabetic patients compared with glucose-tolerant subjects [33]. All these studies described concentric remodelling and LV hypertrophy associated with diabetes mellitus, independent of other confounding factors such as age, obesity (BMI) and hypertension. However, more recently, the NOMAS Study
described diabetes mellitus as an independent determinant of LV mass but in addition to central obesity as assessed by waist circumference [34].

Impact of diabetes on left ventricular remodelling

The impact of diabetes mellitus on LV remodelling over the course of a lifetime has been demonstrated more recently. Indeed, the Framingham Heart Study investigators showed, in a first report, an increase in LV mass during a 16-year follow-up [38]. Diabetic subjects (without heart failure or previous myocardial infarction) experienced a steeper increase in LV mass with advancing age than non-diabetic subjects [38]. In a second report, Cheng et al. [39] demonstrated an increase in wall thickness with advancing age associated with a decrease in LV diameter and a concomitant increase in fractional shortening. This study pointed out the influence of diabetes mellitus, in addition to sex and hypertension, on LV remodelling over life. Indeed, diabetes mellitus was associated with a greater increase in wall thickness coupled with a smaller decrease in LV diameter [39].

Finally, Markus et al. [40] also reported the influence of diabetes mellitus on LV remodelling. During a 10-year follow-up in a population-based cohort of 1005 subjects, the authors observed a greater increase in LV mass in patients with prevalent diabetes mellitus associated with an increase in LV end-diastolic diameter, whereas this last variable remained stable over time in euglycaemic subjects [40]; this was associated with a decrease in LV ejection fraction in prevalent diabetic subjects whereas an increase was observed in euglycaemic subjects [40].

Functional abnormalities

Longitudinal systolic impairment

Myocardial strain imaging, such as TDI and STI, is useful for detecting ischaemia [41]. These techniques also facilitate demonstration of subclinical impairment of systolic function in asymptomatic diabetic patients without overt heart disease and a normal standard echocardiography compared with controls [23,42–50]. Whereas conventional methods such as LV ejection fraction and fractional shortening were insensitive in terms of detecting early preclinical abnormalities, longitudinal dysfunction was demonstrated in many studies using both TDI [23,42,44,45,48–50] and STI [43,46,47]. For some authors, longitudinal strain decrease was correlated with diabetes imbalance (glycated haemoglobin) or microvascular complications (microalbuminuria) [50]. However, longitudinal alteration is independently associated with diabetes mellitus, regardless of LV hypertrophy [23] or other conventional risk factors [43].

Radial systolic impairment

Radial systolic function has been investigated less frequently in this population. Indeed, only a few studies have assessed radial function, with conflicting results [43,44,46,47,50]. The initial studies suggested that radial function was increased [44,50] or preserved [47] to compensate for longitudinal function alteration. However, most of these studies were based on TDI and its derived velocity and strain rate measurements that depend on Doppler angle [44,50]. The TDI measurements are limited to the segments in which motion and deformation are aligned with the ultrasound beam and hence do not provide an optimal evaluation of radial function. STI is an angle-independent method and allows a more robust and extensive evaluation of radial function (Fig. 2) [51]. Among reports based on STI, the study by Ng et al. [47] described preserved radial function compared with euglycaemic subjects (radial strain 40.6 ± 11.1 vs. 42.7 ± 12.1%, respectively; P not significant). However, this study was based on a highly selected population that included uncomplicated patients and only men with a short duration of diabetes mellitus (4 years) and a strictly controlled haemoglobinA1c concentration (6.4 ± 0.7%). Conversely, our group demonstrated in a population of 114 diabetic subjects, a decrease in both radial strain (50 ± 16 vs. 56 ± 12%; P = 0.003) and longitudinal strain (−19 ± 3 vs. −22 ± 2%; P < 0.001) compared with 88 age-matched controls without cardiovascular risk factors [43]. In multivariable analysis, diabetes mellitus was independently associated with longitudinal strain (in addition to sex) and radial strain. These findings remained stable in a subgroup analysis of 42 strictly age-, sex- and BMI-paired patients and controls [43].

Contractile reserve

Whether diabetes mellitus is also responsible for a decrease in contractile reserve in asymptomatic patients without overt heart disease is a controversial issue [50,52–54]. Galderisi et al. [53] demonstrated an impaired inotropic response to dobutamine in 24 diabetic patients compared with 16 controls. With dobutamine, myocardial strain assessed by TDI increased by 36.4 ± 15.9% in diabetic patients vs. 57.1 ± 22.1% in controls (P = 0.0001). Ha et al. [54] showed impairment of longitudinal function reserve (as assessed by mitral annular systolic velocity) during exercise. However, Fang et al. [52] reported a normal response to dobutamine stress, suggesting that ischaemia due to small vessel disease might not be important in early diabetic heart muscle disease.

Diastolic dysfunction

Diastolic dysfunction has been extensively studied in diabetic patients without overt heart disease [55–63]. Prevalence of diastolic dysfunction is high in diabetic patients, ranging from 21% to 75% [55–63]. However, heterogeneity of populations enrolled and methodological issues regarding the assessment of diastolic function account for the highly variable prevalence reported in these studies [55–63]. Indeed, most of the reports were based on one single abnormal variable using mitral inflow pattern [63], its variation with the Valsalva manoeuvre [62] or combined indices derived from mitral inflow pattern and pulmonary venous flow [60]. More recently, some authors analysed TDI diastolic velocities and derived indices [55–58] but only two studies were based on a more complex diagnostic algorithm and a comprehensive evaluation of diastolic function [59,61]. However, in the study of Poulsen et al. [61], including a population of patients with type 2 diabetes mellitus, 9% presented a LV ejection fraction less or equal than 50% and 30% of patients presented perfusion abnormalities assessed by scintigraphy. Kiencke et al. [59] included 100 patients with type 2 diabetes mellitus and explored diastolic function using a comprehensive algorithm close to the current recommendations; they found a
prevalence of diastolic dysfunction of 48%. Recently, in a study strictly based on the current European Association of Echocardiography/American Society of Echocardiography recommendations, our group reported a prevalence of diastolic dysfunction of 47% (33% grade I and 14% grade II).

Diastolic dysfunction has been traditionally considered as the first marker of DCM [56,58,60]. However, whether diastolic dysfunction reported in diabetic patients is an independent adverse effect of diabetes mellitus has been poorly investigated. Indeed, the association between potential confounding factors (such as hypertension, obesity, age...
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and sex) and diastolic function was not taken into account in many studies. We recently demonstrated that in contrast to systolic impairment in diabetic patients, diastolic variables are mainly associated with other factors (including age, rate pressure product, history of hypertension and BMI) and that of the most frequently used diastolic variables (E/A ratio, e’ velocity) are not independently associated with diabetes mellitus [64]. In addition, standard LV systolic variables are mostly insensitive to detecting systolic impairment. When using myocardial systolic strain, we found that 28% of patients presented longitudinal dysfunction with normal diastolic function [64].

Nevertheless, diastolic variables are related to prognosis in diabetic patients without patent heart disease [57–59]. In a first retrospective study, including 486 diabetic patients, From et al. [57] demonstrated that the E/e’ ratio was associated with an increase in global mortality after adjustment for age, sex, coronary artery disease, hypertension, LV ejection fraction, left atrial volume and delay between diabetes diagnosis and echocardiography. In a second retrospective study, including 1760 diabetic patients, the same authors demonstrated that an E/e’ ratio more than 15 was associated with a cumulative probability of development of heart failure at 5 years of 36.9% compared with 16.8% for patients with an E/e’ ratio less or equal than 15 (P = 0.001) and, with a higher global mortality (30.8% vs. 12.1% at 5 years; P < 0.001) [58]. Kiencke et al. [59] confirmed that patients with diastolic dysfunction had a lower overall event-free survival rate than patients without diastolic dysfunction (54 vs. 87%; P = 0.001).

Microvascular alteration
Alteration of microvessels associated with endothelial dysfunction has been described in both experimental models of diabetes [65] and humans [66]. Those abnormalities result in a decrease in myocardial blood flow reserve that has been described using myocardial contrast echocardiography (with dipyridamole and exercise) [67], technetium 99 m sestamibi scintigraphy (with dipyridamole) [68] or positron emission tomography (with dipyridamole or cold pressor test) [69,70]. However, the association between perfusion reserve alteration and myocardial dysfunction remains unclear. Indeed, Moir et al. [67] found no association between systolic strain alteration and perfusion.

Therapeutic perspectives
At the stage of heart failure, treatment of DCM is currently based on common heart failure guidelines [71]. However, the main challenge in this pathology is to develop preventive therapeutic options in order to avoid or delay the progression of early myocardial dysfunction associated with diabetes mellitus to overt heart failure. Indeed, modern imaging techniques allow the detection of adverse effects of diabetes mellitus on the myocardium at a very early preclinical stage but the prognostic value of those alterations needs to be defined in order to develop a preventive strategy for patients at high risk. To date, because of the paucity of the data, no preventive therapy is recommended at the preclinical stage of DCM. Based on pathophysiological mechanisms, renin-angiotensin-aldosterone system antagonists [72,73] or antioxidative therapy [74–76] might be of interest.

Conclusions
In summary, there is much evidence in favour of the existence of DCM:
• post-mortem and histological studies introduced the concept of DCM;
• epidemiological studies demonstrated that diabetes is an independent risk factor for heart failure;
• experimental studies explored the pathophysiology and demonstrated an adverse effect of diabetes on the heart in animal models;
• alteration of myocardial content (myocardial fibrosis and steatosis) was demonstrated with noninvasive techniques;
• and finally, noninvasive imaging (especially echocardiography) demonstrated a preclinical form of diabetic heart disease with subtle alterations in LV morphology, remodelling and systolic and diastolic function.

However, whether the preclinical form of DCM is of prognostic significance and leads to overt heart failure with increased mortality remains to be investigated. In addition, prevention therapies that could avoid the evolution to overt heart failure need to be defined.

Disclosure of interest
The authors declare that they have no conflicts of interest concerning this article.

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