

Diabetic cardiomyopathy, does it exist?

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Abstract

Diabetes mellitus markedly increases the risk for cardiovascular disease, including the risk for the development of heart failure (HF). This HF risk remains increased even after adjustment for coronary artery disease (CAD) and hypertension. Thus, the term diabetic cardiomyopathy (DC) was coined, defined as ventricular dysfunction in the absence of CAD and hypertension. While the literature about the effects of diabetes on the myocardium is increasing, a controversial discussion on the existence of DC persists. Studies both in animals and humans need to be considered to evaluate whether DC exists, and to reconsider how appropriately the term “diabetic cardiomyopathy” actually describes the direct effects of diabetes on the myocardium. In addition, type 1 and type 2 diabetes mellitus likely differentially affect the heart, which is not considered in the definition of DC. In the following article, I will briefly review the controversial discussion and arguments that may support or reject the hypothesis of the existence of DC, including the effects of the distinct types of diabetes mellitus on the myocardium. ■ *Heart Metab.* 2015;68:35-38

Keywords: diabetic cardiomyopathy; diabetes mellitus; heart

In diabetes, the risk of heart failure (HF) is increased despite adjustment for coronary artery disease (CAD) and hypertension. Thus, the term “diabetic cardiomyopathy” (DC) was introduced to refer to this cardiac entity, defined as ventricular dysfunction in the absence of CAD and hypertension. While the evidence in the literature supporting the existence of DC is increasing, the debate about its existence remains controversial. Some discussion may result from the term “diabetic cardiomyopathy” per se, which may describe the effect of diabetes on the myocardium in a somewhat inconvenient way, since the conventional criteria of a cardiomyopathy, which includes ventricular dilation and impaired systolic function, are usually not met by DC. In the following paragraphs, I will briefly review the controversial

discussion and the arguments that may support or reject the hypothesis of the existence of DC, including the effects of the distinct types of diabetes mellitus on the heart (*Figure 1*).

Diabetic cardiomyopathy in type 2 diabetes mellitus?

Numerous studies report an increased risk for HF in type 2 diabetic subjects despite adjustment for CAD, hypertension, age, sex, cholesterol, and body weight.¹ Furthermore, Iwasaka and colleagues showed that the regional ejection fraction of the noninfarcted area following myocardial infarction is decreased in type 2 diabetic subjects, although global ejection fraction is not significantly reduced. This suggests that the non-

Abbreviations

CAD: coronary artery disease; **DC:** diabetic cardiomyopathy; **HF:** heart failure; **HFPEF:** heart failure with preserved ejection fraction; **IVRT:** isovolumic relaxation time; **LV:** left ventricular

infarcted area is unable to compensate for the loss of function in the infarcted area.² Finally, Jaffe et al report a markedly increased incidence of pulmonary congestion in type 2 diabetic patients with previous myocardial infarction despite smaller myocardial infarct size in the diabetic cohort.³ These observations support the idea of an increased myocardial vulnerability in type 2 diabetes mellitus. The clinical features of DC are thought to include left ventricular (LV) hypertrophy and diastolic dysfunction. Diastolic dysfunction remains significant after adjustment for CAD, hypertension, and LV mass index, and this seems to be true even for subjects with insulin resistance, although several studies reported that a significant association of diastolic dysfunction and type 2 diabetes mellitus disappeared after adjustment for comorbidities.^{4,5} LV hypertrophy and diastolic dysfunction may increase the risk for pulmonary congestion and edema due to HF with preserved ejection fraction (HFPEF), which accounts for up to 50% of HF cases in the nondiabetic population. This may be particularly true if additional stressors are present in diabetic subjects, such as ischemic cardiomyopathy, hypertension, or impaired vascular dynamics. While there is no convincing evidence of a reduced ejection fraction in DC

in type 2 diabetic patients, more sensitive measures of systolic function such as strain analysis have recently been reported to detect subclinical impairment in longitudinal and radial strain, suggestive of a mild impairment due to diabetes itself.⁶

More support for an adverse effect of diabetes on the myocardium comes from studies in rodent models. Many of these models develop cardiac dysfunction, including systolic impairment of contractile function.⁷ Since rodents are somewhat resistant to the development of CAD, this cardiac dysfunction may primarily be considered a direct effect of the diabetes-associated metabolic milieu on the myocardium. Molecular alterations in hearts of type 2 diabetic rodents include oxidative stress, increased fibrosis, alterations in myocardial energetics, impaired calcium handling, and increased inflammation, among many others.⁷ Interestingly, many of these alterations have also been observed in failing hearts, suggesting that preexisting molecular alterations in DC may indicate an already predisposed and vulnerable myocardium that may ultimately progress to overt HF if sufficient additional stressors are present. Furthermore, genetically modified mice mimicking specific effects of the diabetic milieu on the heart were helpful to clarify that and how systemic metabolic alterations (eg, hyperglycemia, hyperlipidemia, and insulin resistance) affect the heart in type 2 diabetes mellitus.⁷ Finally, it is important to mention that the few human studies that are now available confirm findings of rodent DC in human hearts, including increased oxidative stress, mitochondrial dysfunction, and altered energy substrate metabolism.^{8,9}

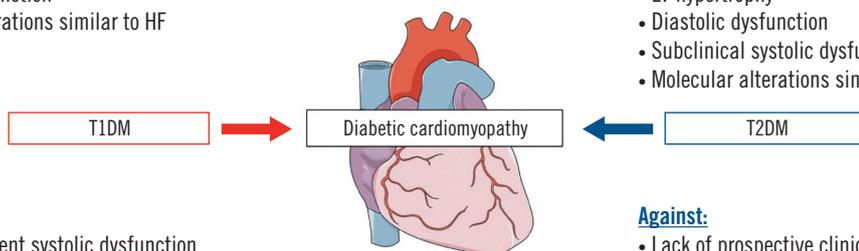
Arguments for and against the existence of diabetic cardiomyopathy

For:

- Increased HF risk
- Diastolic dysfunction
- Molecular alterations similar to HF

For:

- Increased HF risk
- LV hypertrophy
- Diastolic dysfunction
- Subclinical systolic dysfunction
- Molecular alterations similar to HF



Against:

- Lack of persistent systolic dysfunction
- Diastolic dysfunction persistent after multivariate adjustment?
- No significant cardiac dysfunction in long-term T1DM
- Unspecific effects due to exogenous insulin treatment?

Against:

- Lack of prospective clinical trial
- Secondary effects due to hyperinsulinemia and RAAS?
- Systolic/diastolic dysfunction not specific to diabetes?
- Prognosis of subclinical cardiac dysfunction unclear

Fig. 1 A summary of arguments that may support (for) or reject (against) the hypothesis of the existence of diabetic cardiomyopathy in type 1 and type 2 diabetes mellitus.

Abbreviations: HF, heart failure; LV, left ventricular; RAAS, renin-angiotensin aldosterone system; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

A major criticism regarding the existence of DC in type 2 diabetes mellitus is the lack of a prospective clinical trial showing an increased risk for HF and/or impaired cardiac function in the complete absence of confounders, eg, CAD and hypertension. However, such a study would be costly, would require a rather long-term follow-up period, and would need a large amount of patients since many diabetic patients will develop confounding comorbidities during the course of such a trial, thus making it unlikely that we could expect data on the subject anytime soon. It has been argued that the changes in diastolic function may be attributable to an increase in peripheral resistance and myocardial overload mediated by hyperinsulinemia and secondary activation of the sympathetic nervous system. Since insulin acts as a growth factor, it has been suggested that the increase in LV mass in type 2 diabetes mellitus may be due to hyperinsulinemia.¹⁰ Some authors argue that subclinical systolic and diastolic dysfunction that can only be detected with strain imaging is observed in many other conditions, including obesity, hypertension, and even healthy aging. Therefore, such findings, even when present, may not be specific to diabetes. Whether the subclinical form of DC is of prognostic significance still remains to be investigated.

Diabetic cardiomyopathy in type 1 diabetes mellitus?

One study has shown the risk for the development of HF to be increased in type 1 diabetic subjects, with duration of diabetes and impaired glycemic control predictive of HF.¹¹ In that study, hospital admission for HF occurred in almost 1 in 30 fairly young patients with type 1 diabetes mellitus, implying that HF was a major diabetic complication in these patients.¹¹ In another study, the incidence of HF in type 1 diabetic patients aged 41 to 45 years was reported to be similar to that in nondiabetic patients aged 55 to 64.¹² Similarly, it has been proposed that diabetes alone may lead to premature aging of the heart (as a sign of DC), since values of some echocardiographic parameters of diastolic function measured in young (20-32 years) persons with type 1 diabetes mellitus correspond with the diastolic parameters of healthy men at the age of 50 and over.¹³

Evaluating the impact of type 1 diabetes mellitus on cardiac function has been challenging, probably

related to the fact that patient selection and exclusion criteria may have varied considerably between studies. While only a few studies demonstrate actual systolic dysfunction in type 1 diabetic patients, studies frequently report normal or increased LV systolic function.¹⁴⁻¹⁶ Most studies observe abnormal LV diastolic function, whereas some report no evidence of LV diastolic dysfunction at rest in long-term type 1 diabetes mellitus.^{17,18} It remains controversial whether diastolic dysfunction is due to diabetes per se, since adjustment for coexistent hypertension, CAD, autonomic dysfunction, and microangiopathy blunt the significance for diastolic dysfunction in some studies.¹⁷

A recent study that observed type 1 diabetic patients over an average of 36 years demonstrated that the HF incidence was rather low, and HF and myocardial dysfunction were only observed if patients developed hypertension or CAD.¹⁹ Despite the presence of microvascular dysfunction and fibrosis, no significant echocardiographic differences were observed in long-term type 1 diabetes mellitus in another study.¹⁰ Thus, rather recent studies may argue against a relevant effect of type 1 diabetes mellitus on cardiac function. The lack of cardiac dysfunction may be related to permanent treatment with exogenous insulin, which treats potentially causative systemic metabolic alterations. It has also been argued that myocardial overload and increased peripheral resistance after the administration of exogenous insulin may cause diastolic dysfunction, as opposed to being symptoms of DC. Others discussed that in some studies, echocardiographic parameters used to diagnose diastolic dysfunction (eg, shortened E/A ratio, prolonged isovolumic relaxation time [IVRT]) were misinterpreted, since absolute values that were significantly different between diabetic and nondiabetic subjects were actually (according to echocardiographic guidelines) within the normal range for healthy people, which would not allow a diagnosis of diastolic dysfunction in the diabetic cohort.

In animal models of type 1 diabetes mellitus, cardiac dysfunction has been observed in most studies, and molecular alterations are similar to that seen in type 2 diabetic hearts, including oxidative stress, increased fibrosis, alterations in myocardial energetics, impaired calcium handling, and increased inflammation, among many others, although some differences to type 2 diabetes mellitus models exist.⁷ Such differ-

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ences may be related to the different pathophysiology, such as differential effects of insulin deficiency in type 1 versus insulin resistance in type 2 diabetes mellitus on cardiomyocyte insulin signaling and downstream pathways. While animal studies support the existence of DC in type 1 diabetes mellitus, it needs to be considered that diabetic animals are usually not treated with insulin. Thus, exacerbated hyperglycemia and insulin deficiency both have a continuous impact on the heart. In contrast, even though glycemic control may vary between subjects taking insulin, insulin treatment does exist in humans, and this may ameliorate the effects both of hyperglycemia and insulin deficiency on the myocardium.

Conclusions

To answer the question of whether DC exists may require appropriate interpretation of a large amount of available literature on the topic and careful reconsideration of the actual meaning of the term “diabetic cardiomyopathy.” Taken together, animal and human studies show overwhelming evidence of DC in type 2 diabetes mellitus, which is a combination of various molecular alterations within the myocardium, and which may be considered a predisposition to develop HFPEF and potentially also systolic dysfunction. However, data from a prospective clinical trial to more clearly evaluate the latter issue is not yet available. Molecular alterations and cardiac dysfunction also occur in animal models of type 1 diabetes mellitus, but the interpretation of data in humans is complicated due to considerable differences in patient selection and exclusion criteria and because patients are treated with insulin, which likely ameliorates the effect of type 1 diabetes mellitus on the heart. ■

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