TITLE: DIABETIC CARDIOMYOPATHY

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Learning Objectives

- Recognise proposed definitions of diabetic cardiomyopathy and debates about its existence
- Appreciate the proposed effect of diabetes on the heart via various pathophysiological mechanisms (although not all fully understood)
- Understand the adverse impact of clinical outcomes of diabetes on heart failure (and vice versa)
- Be aware of the need for further evidence in this area (especially in patients with diabetes and in those with diabetes and heart failure)

Introduction

Heart failure in patients with diabetes has been recognised since 1876 [1]. The cardiovascular harm of thiazolidinediones shone the 21st century spotlight on the interaction between these two conditions [2,3]. Recent clinical trials reporting cardiovascular benefit of drugs used to treat diabetes have sparked even more interest [4–7]. The phrase "diabetic cardiomyopathy" entered the literature in 1972 [8]. Over subsequent years there has been a steady increase in the use of the term. There is debate about the existence of a distinct diabetic cardiomyopathy.

Definition of "diabetic cardiomyopathy"

The key challenge is the lack of a universally-accepted and consistently-applied definition (Table 1) [1,8–21]. Liu reports on a condition in which there is ventricular dysfunction in the **absence** of coronary artery disease [22]. Boudina and Rydén (including the European Society of Cardiology in collaboration with the European Association for the Study of Diabetes) require the **absence** of both coronary artery disease and hypertension [11,18]. Tarquini and Aneja suggest that not only should both coronary artery disease and hypertension be **absent** but other cardiovascular conditions (e.g. valvular heart disease) should be absent as well [12,16]. Fang and Boudina do not require the **absence** of these conditions but only that cardiac dysfunction cannot be **"ascribed"** to or be **"directly attributable to"** other causes of cardiac disease [10,14].

Another aspect of the definition for which there is no agreement is exactly what the pathognomonic cardiac consequences of diabetic cardiomyopathy are. Voulgari and Lorenzo-Almorós have described it as a condition that requires ventricular dilatation or interstitial fibrosis **and** hypertrophy **and** a decrease in systolic **and** diastolic function of the **left** ventricle [15,21]. Rydén and Fang refer more generally to diabetic cardiomyopathy causing "ventricular dysfunction" or "myocardial disease" [10,18]. There are many unanswered questions. Before a diagnosis of diabetic cardiomyopathy is made, what cardiac abnormalities should be present? Must there be left ventricular abnormalities of diastolic and/or systolic function. Does an echocardiogram that reveals no abnormalities mean that a patient does not have diabetic cardiomyopathy or is a lack of abnormality by cardiac magnetic resonance imaging necessary? Is it possible that metabolic abnormalities of the heart could be seen (for example, on phosphorus-31 magnetic resonance spectroscopy) (possibly a precursor) in the absence of structural changes?

Diabetes is diagnosed after a specific glycaemic threshold is reached, dividing a continuous measure (glucose and glycated haemoglobin) into a categorical one. To define a condition by an arbitrary glycaemic cut-off can be debateable – unless it is the treatments for diabetes that cause the heart failure (because they are only given when the threshold is crossed).

A further challenge is illustrated by the clinical scenario of co-incidentally occurring "idiopathic" dilated cardiomyopathy and diabetes. Diabetes is common in the general population and heart failure also increases the risk of diabetes. How does a clinician determine whether cardiac dysfunction is due to diabetes or is actually a dilated cardiomyopathy with another cause? A related dilemma is illustrated by two contrasting presentations of heart failure and diabetes. One patient may have had diabetes for twenty years but heart failure for only two years while the other has had heart failure for five years and diabetes for two years. It seems likely that the first patient could have a contribution of diabetic-related cardiac disease (or "diabetic cardiomyopathy") while the second patient is much less likely to. The Bradford Hill criteria for causation could be explored [23].

It seems unrealistic to require the absence of coronary artery disease, hypertension or any other form of cardiac disease before a diagnosis of diabetic cardiomyopathy is made. For example,

hypertension is common in the general population hence to require its absence would frequently prevent a diagnosis of "diabetic cardiomyopathy" being made. The American Heart Association, American College of Cardiology, the Heart Failure Association of the European Society of Cardiology and American Diabetes Association have not yet defined "diabetic cardiomyopathy". Current definitions are inconsistent. We think it is very likely that diabetes does have cardiac effects but these are likely to occur most often alongside other concurrent processes and much less often in isolation. We propose that "diabetic cardiomyopathy" should be defined as: "cardiac abnormalities not wholly explained by other cardiovascular or non-cardiovascular causes and likely to be due to diabetes. Diabetic cardiomyopathy most often occurs alongside other cardiovascular conditions but may occur as the sole cause of cardiac disease" (Figure 1).

Type 1 versus type 2 diabetes

Most of the current understanding of the cardiac effects of diabetes relates to type 2 diabetes. It has been proposed that diabetic cardiomyopathy might be a result of different pathophysiological processes in type 1 compared with type 2 diabetes [24]. Autoimmunity may be partly responsible for type 1-related cardiac abnormalities, whereas hyperglycaemia, hyperinsulinaemia, insulin resistance and other comorbidities such as obesity, hypertension and dyslipidaemia may be more important contributors to type 2-related cardiac abnormalities [24,25]. The rest of this manuscript refers to type 2 diabetes only.

Proposed sub-groups of diabetic cardiomyopathy

Subgroups of diabetic cardiomyopathy have been proposed. Maisch (Table 2) [10,26] suggested four stages of diabetic cardiomyopathy with each stage representing a more progressive form of the process from heart failure with preserved ejection fraction to heart failure with reduced ejection fraction. Patients with stage 1 diabetic cardiomyopathy have no symptoms and only diastolic dysfunction. Abnormalities of diastolic and systolic function are described in stages 2 and 3. Patients in stage 4 have symptomatic heart failure and dilated hearts characterised by fibrosis and disease of large and small coronary arteries. There appear to be many clinical presentations that do not fit neatly into these classes. If a patient with heart failure, reduced ejection fraction and epicardial coronary artery disease has "diabetic cardiomyopathy" this is would be at odds with some previously mentioned definitions. The finding of late gadolinium would suggest myocardial infarction which is said to be "very frequent" in stage 4. Does this mean that the myocardial infarction is a feature of diabetic cardiomyopathy and occurs independently of coronary artery disease? Elevated troponins are said in stage 4 to be "positive in infarction". Are these infarctions due to diabetic cardiomyopathy and not myocardial infarction? With regard to the findings on echocardiography and myocardial biopsy the evidence for these in humans with diabetic cardiomyopathy is not clear. We suggest that clinicians should consider the relative role that diabetes plays (compared to other factors) in each patient with both diabetes and heart failure.

Seferović described two distinct phenotypes (restrictive/heart failure with preserved ejection fraction and dilated/heart failure with reduced ejection fraction) [24]. The challenge in applying these two subgroups to patients in clinical practice is to know when abnormalities of the myocardium or coronary artery are due to diabetic cardiomyopathy or when they are due to concurrent processes unrelated to diabetes or to coronary artery disease.

Epidemiology of diabetic cardiomyopathy

With no universally accepted definition, it is not possible to determine the incidence or prevalence of diabetic cardiomyopathy. One argument that has been made in favour of a specific diabetic cardiomyopathy is that the higher incidence of heart failure in patients with diabetes persists after

correction for hypertension and coronary artery disease [26,27]. A review of the epidemiology of the heart failure and diabetes in general is beyond the scope of the current manuscript.

In clinical trials of heart failure with reduced ejection fraction, the number of patients with an investigator-designated diabetic aetiology (which may be interpreted as "diabetic cardiomyopathy") is very small (<1% in both PARADIGM-HF and CHARM) [28–30].

Incidence and prevalence of heart failure in patients with diabetes

In primary care in the United Kingdom, heart failure is the second most common incident cardiovascular disease in patients with diabetes (less common than peripheral vascular disease but more common than myocardial infarction) [31]. In the Heart and Soul study, diabetes was an independent predictor of heart failure in patients with stable coronary artery disease [32]. An American study reported a higher prevalence of heart failure in patients with diabetes (11.8%) compared to without diabetes (4.5%) [33]. In Iceland, the prevalence of heart failure in patients aged 33-84 years with and without diabetes was 11.8% and 3.2% respectively [34]. Remarkably, a Dutch study reported that 28% of patients with diabetes had undiagnosed heart failure (European Society of Cardiology diagnostic criteria) [35].

Incidence and prevalence of diabetes in patients with heart failure

The incidence of diabetes in patients with heart failure in the CHARM trial was 7.8% over 2.8 years [36]. The prevalence of diabetes in patients with heart failure in both population-based cohorts and clinical trials is consistently between 25-40% [37–39].

Unrecognised diabetes and pre-diabetes are also common in patients with heart failure. For example in PARADIGM-HF, 13% and 25% had unrecognised diabetes and pre-diabetes respectively [38].

Prognostic implications of diabetic cardiomyopathy

The presence of heart failure in patients with diabetes is associated with worse symptoms and quality of life and higher mortality [37,40,41]. Similarly, the presence of diabetes in patients with heart failure is associated with worse symptoms and quality of life and higher rates of heart failure hospitalisation and mortality [37,38]. The adverse prognosis related to diabetes is seen in both heart failure with preserved and reduced ejection fraction [42]. To what extent these general findings in patients with diabetes and heart failure are due to the process of diabetic cardiomyopathy is unclear. It has been argued that some of the risk associated with diabetes is due to the drugs used to treat diabetes (for example thiazolidinediones cause sodium and water retention) [37].

Pathophysiology

There are a wide variety of mechanisms proposed to be involved in the process underlying diabetic cardiomyopathy (Figures 2 and 3) [21] including epicardial and microvascular coronary artery disease, diabetes-induced myocardial disease (independent of other cardiovascular processes) and diabetic autonomic neuropathy.

Most studies have been conducted in animals rather than humans. Data from animal models of diabetes do demonstrate relatively compelling structural, functional and metabolic cardiac changes that might be relevant in humans with diabetes [43]. However, in this manuscript, we will focus on evidence for diabetic cardiomyopathy in humans. Various processes have been implicated in the pathophysiology of diabetic cardiomyopathy.

Advanced Glycation End (AGE) products

AGE products are proteins or lipids that become glycated after exposure to sugars [44]. There are sparse data in humans to confirm or refute their role in the pathophysiology of diabetic cardiomyopathy. In Netherlands, 64 patients with diabetes, heart failure with both reduced and preserved ejection fraction with unobstructed coronary arteries had higher AGEs on myocardial biopsy compared to those with heart failure without diabetes [45]. While coronary artery disease was excluded, other causes of heart failure, hypertension and other cardiovascular diseases were not excluded. In 205 patients with heart failure with reduced ejection fraction (49 with diabetes), AGE levels in skin (cardiac tissue was not studied) were greater in patients with diabetes compared to those without [46]. This was not a study of patients with a distinct diabetic cardiomyopathy (the majority of patients had coronary artery disease and many had hypertension).

Fibrosis

Fibrosis has been proposed as a key pathophysiological process in diabetic cardiomyopathy but again there are few data in patients to support this hypothesis [47]. In 1972, a post-mortem study of 4 patients with diabetic glomerular sclerosis found left ventricular fibrotic strands and cardiomyocyte hypertrophy on both macroscopic and microscopic examination [8]. In 1993, 12 patients with diabetes (but without coronary artery disease) had more collagen on myocardial biopsy than controls without diabetes [48].

Lipids

Heart failure with preserved ejection fraction patients have a ‘predisposition phenotype’ of being overweight or obese in >80% of cases [49].

Samples of left ventricle and septum from 17 patients with diabetes reveal higher triglyceride and cholesterol concentrations when compared to 9 non-diabetic controls of similar age [50]. Left ventricular tissue was obtained during cardiac transplantation from 27 patients (including 10 with type 2 diabetes) with non-ischaemic heart failure, with the highest levels of intramyocardial lipid staining found in patients with diabetes and obesity (body mass index > 30) [51].

Several magnetic resonance imaging and proton magnetic resonance spectroscopy studies have found associations between diabetes and cardiac steatosis. In 134 individuals in Texas, compared with lean subjects, myocardial triglyceride content was higher in those with impaired glucose tolerance and type 2 diabetes [52]. A Dutch study found increased myocardial triglyceride content in 38 patients with type 2 diabetes compared to 28 healthy controls [53].

Obesity is closely related to diabetes, and is associated with left ventricular hypertrophy. Perhaps the relative natriuretic peptide deficiency (adipose tissue contains natriuretic peptide clearance receptors) in obesity could be a factor in the mechanism of cardiac disease observed in patients with diabetes [54]. The relationship between “diabetic cardiomyopathy” and “obesity cardiomyopathy” is not clearly understood [55].

Myocardial metabolism

Abnormalities of myocardial metabolism have been implicated in the pathogenesis of diabetic cardiomyopathy [56–58]. Whether or not these contribute to the pathogenesis of diabetic cardiomyopathy is unclear.

Vascular and renal changes in diabetic cardiomyopathy

The focus of research into the pathophysiology of a diabetic cardiomyopathy has been the heart. It does seem likely that any process of heart failure in patients with diabetes also involves blood

vessels and kidneys. Investigation of the respective roles of the heart, blood vessels and kidneys in the pathophysiology of diabetic cardiomyopathy has been neglected. Patients with diabetes and nephropathy have a greater risk of incident heart failure than any other population [3].

Cardiac structural and functional changes in diabetic cardiomyopathy

Patients with diabetes but without heart failure

Patients with diabetes but without overt heart failure often have abnormalities of diastolic function and subclinical systolic dysfunction [59,60]. Some have found changes only after stress [61]. Abnormalities of diastolic function can occur in patients with diabetes in the absence of hypertension [12]. Whether these early suggestions of cardiac dysfunction relate to a distinct diabetic cardiomyopathy or to concurrent conditions is not clear. Perhaps the most persuasive evidence of a distinct diabetic cardiomyopathy is a cardiac imaging study from Australia [62]. In this study, abnormal myocardial peak systolic strain, systolic and diastolic velocity were identified in patients with diabetes even after exclusion of left ventricular hypertrophy and coronary artery disease (although this was only excluded by stress echocardiography) [62]. Few other cardiac imaging studies of diabetic cardiomyopathy comprehensively exclude alternative cardiovascular pathologies [59,63–67].

Patients with diabetes and heart failure

In trials of heart failure with reduced (STICH) [68] and preserved ejection fraction (I-Preserve) [69], diabetes is associated with higher E/E'. This could be due to diabetes-associated changes in the myocardium or could be due to patients with diabetes having a greater prevalence of hypertension or other concomitant processes. Interestingly, 3 [68,70,71] out of 7 trials [72–75] of patients with diabetes and heart failure with reduced ejection fraction showed a higher mean baseline left ventricular ejection fraction in patients with versus without diabetes. Whether this has anything to do with a diabetic cardiomyopathy is unclear. Maybe patients with heart failure and diabetes are more symptomatic, so are diagnosed earlier or have symptoms at a relatively higher ejection fraction. In CHARM (unpublished data), patients with diabetes have the same severity of heart failure as a non-diabetic, but at a lower ejection fraction. Perhaps abnormalities of diastolic function or wall thickness reflect changes of diabetic cardiomyopathy.

The right heart

In a Serbian/Italian study, 2D and 3D echocardiographic measures of right ventricle and right atrial function were decreased in normotensive patients with diabetes (without heart failure) compared to healthy controls [76]. An analysis of the PIRAMID trial identified reduced right ventricular systolic and diastolic function by cardiac magnetic resonance imaging in patients with uncomplicated type 2 diabetes compared to healthy controls [77].

Diagnosis/Investigations

In the absence of agreement as to what constitutes a diabetic cardiomyopathy, this condition is not currently diagnosed clinically. The European Society of Cardiology heart failure guidelines highlighted 'gaps in evidence' in the understanding of pathophysiology and potential treatments in specific heart failure populations, including diabetic patients [78]. Typical symptoms combined with an elevated B-type natriuretic peptide can indicate the presence of heart failure but not a specific diabetic cardiomyopathy. Similarly, an abnormal echocardiogram or cardiac magnetic resonance imaging can identify structural cardiac abnormalities, but not that these are due to diabetes.

Biomarkers

The roles of many novel biomarkers have been investigated in diabetic cardiomyopathy (Figure 4) [21]. In patients with acute heart failure, levels of many biomarkers have been found to be higher in cohorts of patients with diabetes compared to control subjects [79]. Whether they are indicators of diabetic cardiomyopathy, or are elevated because of the various cardiovascular processes that occur in patients with diabetes is uncertain. Transforming growth factor beta was higher in those with diabetes and diastolic dysfunction than in those with diabetes without diastolic dysfunction [80]. Procollagen type I propeptide levels were higher in patients with newly diagnosed diabetes compared to healthy controls and correlated with diastolic dysfunction [81]. A correlation also has been demonstrated between collagen biomarkers such as matrix metalloproteinase-7 and the presence of asymptomatic diastolic dysfunction in a population of diabetic patients [82].

Therapies for diabetic cardiomyopathy

No therapies have been tested specifically in patients identified as having a diabetic cardiomyopathy. In Venezuela, the addition of sitagliptin for 24-weeks reduced epicardial adipose tissue in patients with type 2 diabetes [83] (although we know that this drug does not prevent heart failure in patients with diabetes) [84]. Once "diabetic cardiomyopathy" is defined, clinical trials can begin. An AGE breaker has been administered to humans in phase 1 clinical studies [85].

Therapies tested in animals

Zinc supplementation [86,87], AGE breakers (aminoguanidine) [88], copper chelators (trientine) [89], metformin [90,91], angiotensin-converting enzyme inhibitors [92,93], beta-blockers (timolol) [94] and dipeptidyl peptidase-4 inhibitors [95] as well as other putative therapies have been tested in animals with some apparently beneficial effects in the respective species reported. None of these have been trialled in patients with diabetic cardiomyopathy.

Prevention of heart failure in patients with diabetes

The recent finding that sodium-glucose co-transporter-2 inhibitors reduce incident hospitalisation for heart failure in patients with diabetes and vascular disease might be interpreted as indicating that they could have a beneficial effect on a diabetic cardiomyopathy [4,5]. The lack of characterisation of the patients, their hearts and the heart failure hospitalisations in these trials means such a conclusion would be premature. There is an absence of effect on incident heart failure hospitalisations of glucagon-like peptide-1 receptor agonists [6,7,96,97], and uncertainty about dipeptidyl peptidase--4 inhibitors [84,98,99]. Several mechanistic trials of new diabetes therapies in patients with heart failure are underway that might shed light on the existence or otherwise of a distinct diabetic cardiomyopathy.

Summary

Diabetes and heart failure are common bedfellows. Diabetes is a major risk factor for the development of heart failure. Major uncertainty exists as to whether diabetic cardiomyopathy is a distinct clinical entity. In the real world, many diabetics have co-existing concomitant conditions that contribute to the cardiovascular abnormalities. A universally accepted definition of diabetic cardiomyopathy is proposed.

Key Points

Take-Home Messages

- A universally-accepted definition of "diabetic cardiomyopathy" is necessary.

- The pathophysiology of diabetic cardiomyopathy may involve vascular and renal as well as cardiac processes.
- Heart failure and diabetes frequently co-exist and adversely affect the prognosis of the other.
- The contribution of a distinct cardiomyopathy to the development of heart failure in diabetes is unclear.
- Cardiac imaging techniques have reported apparent abnormalities in patients with diabetes. Whether or not these are due to a diabetic cardiomyopathy is unclear.

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