World Journal of Cardiovascular Diseases, 2013, 3, 26-32 **WJCD**
http://dx.doi.org/10.4236/wjcd.2013.35A005 Published Online August 2013 (http://www.scirp.org/journal/wjcd/)

Diabetic cardiomyopathy—What do we know about it?

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Received 9 May 2013; revised 12 June 2013; accepted 29 June 2013

ABSTRACT

Diabetic cardiomyopathy is defined as the presence of myocardial dysfunction in patients with diabetes in the absence of coronary artery disease, hypertension, or other known cardiac disease. Diabetes has been shown to affect the heart through various cellular mechanisms leading to enhanced myocardial fibrosis, left ventricular hypertrophy, systolic and diastolic dysfunction. With increasing incidence of type II diabetes mellitus, it has continuously rising health and financial implications in both developed and developing countries. Hyperglycaemia seems to be the main deriving force, and careful glycaemic control as well as early administration of neurohormonal antagonists currently remains the mainstay of therapy. Many newer treatment targets are currently being explored. Here we present a brief review of its pathophysiology, association with heart failure symptoms, and management strategies.

Keywords: Cardiomyopathy; Diabetes; Heart Failure

1. INTRODUCTION

Diabetic cardiomyopathy is defined as the presence of myocardial dysfunction in patients with diabetes in the absence of coronary artery disease and hypertension, or other known cardiac disease [1]. Diabetes has been shown to affect the heart through various cellular mechanisms leading to enhanced myocardial fibrosis, left ventricular hypertrophy (LVH), systolic and diastolic dysfunction [1]. With increasing incidence of type II diabetes mellitus, it has continuously rising health and financial implications in both developed and developing countries. Hyperglycaemia seems to be the main deriving force [2], and careful glycaemic control as well as early administration of neurohormonal antagonists currently remains the mainstay of therapy.

The risk for heart failure (HF) in diabetics independent of other confounding factors is increased upto 2.4:1 in males and 5:1 in females [3-8]. Elevated glycated haemoglobin (HbA1c) is itself associated with an 8% increase in HF incidence [9]. More specifically, up to 75% of asymptomatic normotensive diabetic patients with normal ejection fraction (LVEF) will have diastolic abnormalities [10].

2. PATHOPHYSIOLOGY

Angiographic and autopsy studies have confirmed higher prevalence of cardiomyopathy in diabetics when compared to non-diabetic patients, as well as more extensive disease patterns and more severe proximal and distal CAD [11-18]. With similar infarct sizes, diabetic patients have a far greater risk of developing HF post-myocardial infarction (MI) since the compensatory mechanisms to maintain cardiac output in surviving myocardium, eg hyperkinesis to compensate for non viable myocardium, are not as active due to various intra- and extra-myocardial factors and reduced coronary blood flow [19-23]. There is also enhanced thickening of capillary basement membrane, myocellular atrophy and hypertrophy with myocardial and interstitial fibrosis, which further reduce myocardial function [24-26].

2.1. Hyperglycaemia

Hyperglycaemia is the main trigger factor. One of the principle abnormalities is impaired coronary vasodilation capacity seconday to increased production of AGEs (advanced glycation end-products). Increased generation of mitochondrial free radicals (Reactive oxygen species; ROS) is another mechanism, which affects the contractility [27,28]. Severity of diastolic dysfunction correlates positively with HbA1c levels [9] which may be related to the activity of increased ROS causing increased collagen deposition in the myocardium leading to fibrosis [29,30].

2.2. Fatty Acids

In healthy individuals the energy required for cardiac

function comes from glucose metabolism and free fatty acids (FFAs). Cardiac ischaemia or increased intra-ventricular pressure changes cardiac ATP production to a predominant glucose oxidation [31]. This phenomenon does not occur in diabetic patients and only 10% of the myocardial energy comes from glucose. This is mainly due to depleted glucose transporter proteins (glucose transporter-1 and -4). This results in a more pronounced beta-oxidation of FFAs [32]. Elevated FFAs are associated with insulin resistance and calcium transporter protein dysfunction, both leading to impaired cardiac function. Increased fatty acids are also associated with the activation of proliferation activated receptor-α (PPARα), suspected to promote mitochondrial uncoupling of oxidative phosphorylation [33], a mechanism that reduces myocardial high-energy reserves and contractile dysfunction [34]. Increased intracellular FFAs may directly lead to apoptosis.

2.3. Protein Kinase C

Protein kinase C, an intracellular signalling molecule, is activated in diabetes and can lead to endothelial dysfunction by reducing the concentration of nitric oxide and increasing free radical production. Protein kinase C can also enhance leukocyte adhesion, increase albumin permeability, and impair fibrinolysis [35,36].

2.4. Renin Angiotensin Aldosterone System (RAAS)

In a non-diabetic patient RAAS is activated by myocardial stretch owing to the stretch receptors. In diabetic subjects, however, an upregulation of RAAS occurs despite minimal changes in myocardial loading [37]. It has been suggested that aldosterone and glucose can cause cardiac fibrosis through stimulation of myofibroblast growth in patients with a dysregulated RAAS especially with concomitant hyperglycaemia [38].

2.5. Hypoxia-Inducible Factor-1

Normally, chronic cardiac ischaemia promotes angiogenesis and collateral vessel formation, mainly through hypoxia-inducible factor-1 (HIF-1), a transcriptional regulator complex present in many gene promoters, including vascular endothelial growth factor (VEGF). In diabetic patients, this angiogenic response to myocardial ischaemia is blunted [39] mainly secondary to markedly reduced (40% - 70%) VEGF and its receptors VEGF-R1 and VEGF-R2 as suggested by animal studies.

2.6. Endothelial Dysfunction

Hyperglycaemia results in impairment of endothelial cell nitrous oxide (NO) production, increased production of vasoconstrictor prostaglandins, glycated proteins, endothelium adhesion molecules and vascular growth factors, which cumulatively enhance vasomotor tone and vascular permeability, growth and remodelling [35]. Hyperglycaemia also enhances endothelial cell matrix production, which may contribute to basement membrane thickening [40]. All these changes will cause increased atherosclerosis and reduced collateral circulation formation in diabetic patients, which may explain the increased infarct extension and congestive HF after MI in these patients.

2.7. Arterial Stiffness

It is well established that hypertension and diabetes lead to increased arterial stiffness [29,41] mainly because of endothelial dysfunction. Reduced compliance of the large arteries in turn affect central systolic pressure and LV afterload, resulting in decreased central diastolic and coronary perfusion pressures [42]. These changes will ultimately result in chronic myocardial ischaemia leading to interstitial fibrosis and HF [43].

2.8. Autonomic Neuropathy

Cardiac autonomic neuropathy is associated with diastolic dysfunction in diabetic patients. It starts with an increase in resting heart rate and a loss of heart rate variability. This can influence the chronotropic and inotropic response of the myocardium. Ventricular filling abnormalities are also prevalent in diabetic patients with autonomic neuropathy independent of duration of diabetes, presence of retinopathy, HbA1, or blood glucose levels [44]. A significant correlation has been described between the E/A ratio and autonomic neuropathy [45].

2.9. Disordered Copper Metabolism

Alterations in copper metabolism have also been proposed as an important contributor to the development and progression of diabetic cardiomyopathy. Elevated serum copper levels are found in patients with diabetes, and the highest levels are found in those with microvascular complications and hypertension [46]. Hyperglycaemia can damage the copper binding properties of ceruloplasmin and albumin (the main copper binding proteins in plasma), resulting in increased copper levels in the extracellular matrix [47,48]. Increased copper in the extracellular matrix is thought to activate the oxidation-reduction system, leading to an enhanced production of free radicals resulting in increased oxidative stress and fibrosis [49].

2.10. Stem Cell Involvement

A recent study has proposed that diabetic cardiomyopathy may be a stem cell disease. Increased oxidative stress in diabetes can alter cardiac progenitor cell (CPC) func-

tion, leading to defective cardiac progenitor cell growth and myocyte formation, causing premature myocardial aging, apoptosis and heart failure. It was also noted that cardiac progenitor cell apoptosis and heart failure were ameliorated by ablation of the p66shc gene in an animal model [50].

3. CLINICAL PRESENTATION

Diabetic cardiomyopathy presents with LVH and/or systolic & diastolic dysfunction which can be categorised into 4 stages depending on the symptoms.

3.1. Diastolic Dysfunction in Diabetes

LV Diastolic dysfunction is much more common than initially reported in subjects with well-controlled type 2 diabetes who are asymptomatic for myocardial disease. In a study of well-controlled type II diabetic patients without any evidence of diabetic complications, hypertension, coronary artery disease, congestive heart failure, thyroid or overt renal disease, LV diastolic dysfunction was present in 60% of subjects, of whom 28% had a pseudonormal pattern of ventricular filling (indicating raised filling pressure), and 32% had impaired relaxation [51]. A similar study of young type I diabetic patients without known cardiac disease demonstrated reduced early and increased late peak mitral velocity, as well as prolonged deceleration time and isovolumic relaxation time compared with controls, despite normal LV dimensions and systolic function [52]. Some studies comparing type I and type II diabetes have reported that preclinical myocardial disease is more prevalent in type II diabetes [53, 54].

3.2. Systolic Dysfunction in Diabetes

In the context of diabetic cardiomyopathy, systolic dysfunction occurs late, often when patients have already developed significant diastolic dysfunction. Studies have reported that many of those who have normal LV systolic function at rest may show abnormalities during exercise or dobutamine stress [55,56], indicating that LV systolic reserve is reduced in these patients. Diabetic patients have been shown to have a lower cardiac output during supine exercise than controls, with no difference at rest mainly due to a lower stroke volume [57].

It has been suggested that an abnormal EF response during exercise may be due to alterations in ventricular loading conditions and/or cardiac autonomic innervation rather than to abnormalities of contractility itself. Despite subgroups showing an abnormal EF response to exercise, all patients with diabetes had a normal response to afterload manipulation, normal baseline ventricular contractility as assessed by load- and heart rate-independent end-systolic indexes and normal contractile reserve, as assessed with dobutamine challenge [58].

4. STAGES OF DIABETIC CARDIOMYOPATHY

Clinical symptoms of heart failure such as class 1 dyspnoea, according to the New York Heart Association (NYHA), can be absent at an early stage or may be very mild. Maisch *et al*. [59] have recently proposed the following classification of diabetic cardiomyopathy based on the clinical phenotypes:

4.1. Stage 1 Diabetic Cardiomyopathy

Heart failure with preserved EF (HFPEF) in diabetic patients often associated with hypertrophy without relevant hypertension. Relevant CAD, valvular disease and uncontrolled hypertension are not present.

It is the earliest form of diabetic cardiomyopathy and can be detected in 75% of asymptomatic diabetic patients [10].

4.2. Stage 2 Diabetic Cardiomyopathy

Systolic and diastolic heart failure with dilatation and reduced ejection (HFREF) in diabetic patients excluding relevant CAD, valvular disease and uncontrolled hypertension, although CAD and hypertension could play a minor role. Myocardial infarction or uncontrolled hypertension should not be present.

4.3. Stage 3 Diabetic Cardiomyopathy

Systolic and/or diastolic heart failure in diabetic patients with small vessel disease (microvascular disease) and/or microbial infection and/or inflammation and/or hypertension but without CAD. Hypertension, microangiopathy and viral heart disease with or without myocarditis can be the contributing factors.

4.4. Stage 4 Diabetic Cardiomyopathy

If heart failure may also be attributed to infarction or ischemia and remodelling in addition to stage 3, the term should be heart failure in diabetes or stage 4 diabetic cardiomyopathy.

5. MANAGEMENT OF DIABETIC CARDIOMYOPATHY

5.1. Glycaemic Control

Prompt and appropriate treatment of diabetes is clinically relevant because of its role in the pathogenesis of heart failure. Although there is some data suggesting that poor glycaemic control contributes to myocardial dysfunction, evidence that improvements in glycaemic control are therapeutic are limited. The UKPDS (UK Prospective Dia-

betes Study) failed to show a significant benefit of intensive blood glucose control using either sulphonylureas or insulin on the risk of developing macrovascular disease in patients with Type II diabetes [60]. This study however had significant methodological limitations which merit consideration when interpreting the results [61]. These include that the study was unblinded and continued when no difference was observed at the initial agreed time point for analysis, patients in the diet-only group actually received drug treatment if the fasting plasma glucose was > 15 mmol/l, and at 9 years only 25% of patients were on monotherapy.

Hansen *et al*. [62] more recently showed that both myocardial function and myocardial blood volume were reduced in patients with insulin dependent diabetes, and after administration of C peptide a 12% improvement of function was seen in association with improvements of myocardial blood volume and flow. Similarly in another study, von Bibra *et al*. [63] reported improvements of myocardial function and perfusion with insulin. They also noted that the degree of both mechanical change and perfusion was related to the degree of change of fasting insulin with treatment.

There is some data suggesting that diabetic cardiomyopathy does not develop in patients with tightly controlled type 1 diabetes, supporting an important role for hyperglycaemia in the pathogenesis of diabetic cardiomyopathy [64].

There is not much data currently on the choice of glucose lowering agents in diabetic cardiomyopathy. Glucagon-like peptide-1 analogues have been associated with improvement in hemodynamic variables in diabetic patients without overt heart failure [65]. Improved cardiac parameters were also noted with this agent class post-infarction and in advanced heart failure. Use of thiazolidinediones in the management of patients with diabetic cardiomyopathy is difficult due to complications with fluid overload. As a consequence of unforeseen increase in cardiovascular mortality with thiazolidinedoines therapy, US FDA now mandates that all new hypoglycaemic agents should be trialled for diabetic population.

In general, the choice of glucose lowering approach should be directed towards clinical characteristics, such as the presence or absence renal dysfunction, risk of hypoglycaemia, age, volume status, and concomitant drug therapy.

5.2. Blood Pressure Control

No specific data related to changes of myocardial function in diabetes with improved blood pressure control are available. However improvement in mortality was observed with tight blood pressure control in the UKPDS trial [66], with a 15% reduction of mortality for every 10 mm Hg reduction of systolic blood pressure.

5.3. Treatment of Fibrosis

The important role of the RAAS in the pathogenesis of complications in diabetic patients has been discussed above. There is evidence suggesting that angiotensin converting enzyme inhibitors (ACE inhibitors) can prevent myocardial fibrosis, cardiac hypertrophy, and myocardial mechanical dysfunction associated with diabetic cardiomyopathy [67-69]. ACE inhibitors and angiotensin-1 receptor blocking agents have also been shown to prevent coronary perivascular fibrosis and collagen deposition [70,71]. Evidence also suggests a beneficial effect of aldosterone antagonism in diastolic heart failure by its effects on cardiac hypertrophy and fibrosis [72,73].

5.4. Cross Link Breakers

Fibrillar proteins, such as collagens type I and III, and elastin form an intricate widespread network in the extracellular matrix and provide a basis for maintaining the physical structure of the heart and vessels as well as cardiovascular function. Collagen and elastin fibres are enzymatically cross-linked to form matrix.

In addition to these enzymatically formed cross-links, collagen fibres may be linked non-enzymatically, most notably by formation of advanced glycation end-products (AGEs). In addition to diabetes as mentioned earlier, AGEs are also formed increasingly in hypertension and they accumulate with aging. Various effects of AGEs on cardiovascular structure and function have been described above, forming the basis of breaking AGEs (e.g. alanine aminotransferase 711) as a potential tool in the therapy of cardiovascular injury related to diabetes, hypertension and aging.

Limited animal and human data indicate benefit with cross-link breakers. In studies of aging non-diabetic dogs, cross-link breakers caused a significant reduction (approximately 40%) in left ventricular stiffness, which was accompanied by improvement in cardiac function [74].

Another study in diabetic dogs, cross-link breakers restored LV ejection fraction, reduced aortic stiffness and LV mass with no reduction in blood glucose level, and reversed the up regulation of collagen type I and type III [75].

5.5. Other Novel Therapies Targeting Diabetic Cardiomyopathy

In addition to the above mentioned cross-link breakers, other therapies directed toward prevention and progresssion of diabetic cardiomyopathy targeting either enhanced fibrosis/collagen deposition or alterations in cardiomyocyte metabolism which are still in experimental stages include AGEs inhibitors (e.g. aminoguanidine, alani-

ne aminotransferase 946, and pyridoxamine), copper chelation therapy (e.g. trientine), and modulators of free fatty acid metabolism (e.g. trimetazidine).

Modulators of free fatty acid metabolism have proven useful in the management of angina, but their efficacy on diabetic cardiomyopathy is unknown. Newer agents like Exenatide (recombinant glucagon-like peptide-1,) or Sitagliptin (DPP4 inhibitor) are yet to be studied specifically in patients with diabetic cardiomyopathy despite promising cardiac effects with glucagon-like peptide-1 infusion in mechanistic studies.

6. CONCLUSION

Diabetic cardiomyopathy is common and can present with symptomatic or asymptomatic myocardial dysfunction. With the rising prevalence of diabetes, it has major financial and health implication on the healthcare systems. Many newer treatment targets are being explored showing promising initial results, however, further trials are needed for proven benefits. Careful glycaemic control and early administration of neurohormonal antagonists currently remain the mainstay of therapy.

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