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Review Article

Diabetes and the Heart

Gerald H. Tomkin* and Daphne Owens

Diabetes Institute of Ireland, Beacon Clinic and Trinity College, Ireland

***Corresponding author**
Gerald H. Tomkin, Coillancorraig Lodge, Rocky Valley Drive, Kilmacanogue, Co Wicklow

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Abstract

Treatment of diabetes has improved in recent years and has resulted in reduction in mortality and in particular atherosclerotic heart disease. Heart failure with preserved LV function is becoming more common in obese diabetic and non diabetic patients resulting in recurrent hospitalisation and increased mortality. A major cause may be the decreased fitness and reduction in exercise that often accompanies obesity and Type 2 diabetes. Although hyperglycaemia plays an important part in heart failure with preserved LV ejection fraction the disease may start with a much lower 'abnormal' blood sugar suggesting that our current definition of diabetes should be reconsidered.

ABBREVIATIONS

LDL: Low Density Lipoprotein; Hba1c: Glycated Haemoglobin; MET: Metabolic Equivalent; BMI: Body Mass Index; ESH: European Society Hypertension; ESC: European Society Cardiology; CHF: Congestive Heart Failure; V02 Max: Maximum Oxygen Consumption; LV: Left Ventricular; RV: Right Ventricular; GLUT: Glucose Transporter Type 4; DCCT: Diabetes Control and Complications Trial; EDIC: Epidemiology of Diabetes; EDIC: Interventions and Complications Study Research Group. UKPDS: United Kingdom Prospective Diabetes Study

INTRODUCTION

People with diabetes have a greatly increased risk of death from any cause [1] and particularly of cardiovascular disease [2]. Reductions in cardiovascular outcomes were examined using the Swedish National Diabetes Register from 1998-2012 and followed through 2014. Reductions in cardiovascular events during this time were 40% greater in Type 1 diabetes than in controls. The reduction in death was similar to controls. In Type 2 Diabetes the reduction in cardiovascular events was less but still more than in controls but Type 2 diabetic patients had a smaller reduction in fatality than controls over this period. These results fit well with the more recent results from the same group [3]. They studied more than a quarter of a million Type 2 diabetic patients and compared them to almost 1 and a half million controls over a 5-7 year period. They investigated 5 risk factors: blood sugar control, low density lipoprotein (LDL) cholesterol, blood pressure, cigarette smoking and albuminuria. They found that the risk for death was similar to controls if all 5 variables were within target range. The reduction was stepwise for each variable. An important finding was that glycated haemoglobin (HbA1c) outside range (>53 mmol/mol) was the strongest predictor of acute myocardial infarction and stroke. Not so good news was that the risk of hospitalization for cardiac failure was consistently higher among the diabetic patients as compared to controls even if the risk factor variables were controlled.

A definition of cardiomyopathy is, "a disease of the myocardium that leads to chronic and progressive damage" [4-7]. The purpose of this paper is to review diabetic cardiac disease and to emphasis the role of cardiac myopathy outside and above atherosclerosis which for so many years has been the main focus of attention. It seems to the authors that atherosclerosis and the wonderful benefits of statins, has until recently, obscured the important effect of diabetes on cardiac structure and function and which leads to so many admissions to hospital for treatment of cardiac failure. The evidence is that the reduction in myocardial infarction in the last decades has reduced heart failure with reduced ejection fraction but probably the increase in heart failure with preserved ejection fraction is increasing due to the obesity epidemic [8-10].

The metabolic disturbance in diabetes is considerable and can only be summerised in this short review. Most patients with long standing diabetes will have evidence of atherosclerotic coronary artery disease probably causing some reduction in muscle supply at least in exercise. Patients with cardiac failure and preserved left ventricular function have little or no obvious atherosclerosis of the coronary arteries and the major dysfunction occurs because of non eschaemic cardiomyopathy. The role of diabetic microangiopathy is difficult to define but probably is important in some patients.

The increase in blood sugar and absolute or relative deficiency in insulin with insulin resistance and hyperinsulinaemia, causes an increase in free radical production and an increase in oxidation advanced glycation end products are formed with fibrosis and stiffening of the cardiomyocyte and decreased contractility.

The other major metabolic dysfunction to affect the heart muscle is through the increase in free fatty acids and triglyceride with deposition in the heart and defective metabolism and defective use for energy production.

Micro RNAs are implicated in the dysmetabolism of diabetes and microvascular dysfunction. They have been shown to be involved in cardiomyocyte remodeling and insulin sensitivity. The cardiomyocyte depends on carbohydrate and fat as energy sources. The shift from carbohydrate to fat in diabetes necessitates increased oxygen consumption which may be impaired due to macro or micro vascular insufficiency particularly in exercise. It is for this reason that micro RNAs are of interest as therapeutic targets in cardiomyopathy. For good reviews [11,12]

The RELAX trial [13] enrolled 216 patients with heart failure and an ejection fraction of >50%. Diabetic patients were younger, more obese and had a higher prevalence of hypertension, renal dysfunction, pulmonary disease and vascular disease. Diabetic patients had more ventricular hypertrophy but systolic and diastolic parameters were similar in diabetic and non diabetic subjects except for a trend in higher filling pressures in the Diabetic patients. In the CHARM program [14] it was observed that diabetic patients with heart failure with preserved ejection fraction had a greater relative risk of cardiovascular death or heart failure hospitalization than those diabetic patients with low ejection fraction. However all cause mortality was not influenced by ejection fraction. As long ago as 2007 Karamitsos et al. [15], showed that Type 1 diabetic patients free from coronary heart disease and hypertension had disturbed diastolic function in both ventricles as compared to normal age and sex matched controls. In a more recent paper Gorter et al. [16], examined the relationship between diabetes and right ventricular function in heart failure patients with preserved ejection fraction. They found that diabetes was strongly associated with right ventricular systolic dysfunction independent of right ventricular after load. The ventricular dysfunction is not solely in the right ventricle. Philouze et al. [17], showed that dobutamine stress unmasks early left ventricular dysfunction in asymptomatic patients with uncomplicated type 2 diabetes. They found in 35 patients compared to 35 matched controls no difference in echocardiography results at rest but after dobutamine stress, significant differences appeared. Multivariate analysis showed that epicardial fat, dyslipidaemia and fasting glycaemia were significant contributors to the changes from rest to dobutamine. The difference between Type 1 diabetic patients and Type 2 diabetic patients has been explored by Roberts et al. [18], Their premise was that perhaps the co-morbidities associated with type 2 diabetes such as obesity and sedentary behavior might account for the impairment in exercise. They studied 20 Type 1, 20 Type 2 and 10 controls for each of the 2 diabetic groups. The Type 2 patients were heavier than their controls, took less exercise and had lower exercise capacity. The differences were not associated with biventricular systolic or left ventricular diastolic dysfunction at rest or during exercise. Type 1 patients were similar to controls and had no defect in exercise capacity. Maximum oxygen consumption (VO2peak) was associated with cardiac size and exercise (Estimated MET hours/week) with no evidence of subclinical cardiac dysfunction. This study shows that at least in these patients, sedentary behavior rather than cardiac dysfunction was the cause of poor exercise capacity. Wilson et al. [19], examined whether impaired left ventricular filling or reduced systolic ventricular ejection was responsible for the attenuated stroke volume reserve in people with uncomplicated diabetes. People with diabetes had had reduced peak aerobic capacity and heart rate reserve and worked at lower work loads than non diabetic controls. Left ventricular end systolic volume was not different between groups but end diastolic volume was smaller in people with diabetes during exercise but not at rest.

The role of pulmonary hypertension in the development of right ventricular dysfunction and heart failure has recently been explored by Whitaker et al. [20], They found that an increase in right ventricular after load beyond pulmonary vascular resistance alone might influence right ventricular re-modeling and provide a mechanistic link between the susceptibility to right ventricular dysfunction in patients with both diabetes and pulmonary arterial hypertension. At the same time the ARIC study [21] reported on the relationship between deteriorating lung function and incident heart failure. The study found that a rapid decline in lung function was indeed associated with a subsequent higher incidence of CVD particularly incident heart failure again suggesting the importance of pulmonary disease driving right ventricular heart failure. Impaired pulmonary function in recently diagnosed Type 2 diabetes has been described [22]. Compared to overweight controls of similar BMI the recent onset type 2 diabetic patients had reduction in pulmonary function with a negative significant relationship between HbA1c and FEV1/FVC.

The pathological hall mark of diabetic complications is microvascular damage as seen in diabetic retinopathy, and nephropathy. In 1972 Rubler et al. [23], examined post mortem findings on 27 patients with proven diabetic glomerulosclerosis. Twenty three cases were excluded because of complicating conditions such as hypertension, significant obstruction of the major coronary arteries or valvular disease. Four patients demonstrated cardiomegaly and congestive heart failure of no known cause. Diffuse fibrotic strands extending between bundles of muscle fibres and myofibrillar hypertrophy were found. In one case the small intramural coronary arterioles demonstrated thickening of the wall and narrowing of the lumen due primarily to the deposition of acid mucopolysaccharide material in the subendothelial layers and subsequent subintimal thickening and medial hypertrophy. The authors postulated that the myocardial disease seen was probably due to diabetic microangiopathy.

The prevalence of coronary microvascular dysfunction has been examined recently [24] in a prospective observational study. Two hundred and two patients with heart failure and preserved ejection fraction were recruited from 278 eligible subjects. Fifty one patients had no evidence of coronary microvascular dysfunction and 151 had coronary microvascular dysfunction. Surprisingly, diabetes was present in the same percentage in both groups (25% versus 30% P = 0.5). BMI was significantly higher in the patients with normal capillary microvascular function rather than the other way round. Urinary albumen to creatinine ratio was significantly higher in the patients with coronary microvascular dysfunction. The study raises the question as to the difference between endothelial dysfunction and diabetic microvascular damage as seen in the eye and kidney. This study does not support a role of diabetes and hyperglycaemia in heart failure with preserved ejection fraction. .A study reported by Rozenbaum et al. [25], examined 7000 subjects by Echocardiography. Metabolically healthy obese subjects were

more likely to have diastolic dysfunction. The authors suggest that their findings should be followed up to see whether the diastolic dysfunction will be translated into clinical events and have clinical implications. It is noteworthy that current ESH/ESC guidelines do not include left ventricular diastolic dysfunction in cardiovascular risk charts. This seems reasonable at the present time. Six hundred and ten patients in the Care North study [26] who had hypertension and were free from overt cardiovascular disease were examined by Echocardiography. Left ventricular dysfunction was graded into 3. No subject had grade 3 (the worst grade), 19% had grade 2 and 24% grade 1, 49% had normal diastolic function. Independent variables were female gender, advanced age, obesity, diabetes mellitus and higher systolic blood pressure. Thus diastolic dysfunction in treated hypertensive patients who are asymptomatic is very much more common than expected.

Baldi et al. [27], examined ventricular filling during sub maximal exercise in diabetic patients and compared to non diabetic controls. The reason for the study was based on the findings that LV stroke volume fails to increase or increases less during exercise in patients with diabetes [28,29]**.** They found that the patients with diabetes had an attenuated increase in stroke / volume during exercise due to an inability to maintain /increase LV filling at higher heart rates. The suggestion is that these findings may be due in part to reduced ventricular compliance and decreased time in diastole [30]**.**

Type 2 diabetes and heart failure was recently explored by Johansson et al. [31], in an observational study of more than 30000 patients on the Swedish Heart Failure Registry. Twenty two % had heart failure with preserved ejection fraction, 21% with mid range ejection fraction and 57% had heart failure with reduced ejection fraction. The proportion of patients with type 2 diabetes in each category was similar. Patients with type 2 diabetes and heart failure with preserved ejection were older, often female and burdened with hypertension and renal impairment compared to patients in the other 2 groups. Type 2 diabetes was an independent predictor of mortality among all 3 groups. A systematic review and meta analysis of the prevalence of left ventricular diastolic dysfunction and heart failure with preserved left ventricular function has found that the prevalence is similar between men and women but heart failure is more common in women [32]

The above studies tie in well with the knowledge that obesity, even without diabetes, is a risk factor for heart failure not associated with atherosclerotic heart disease [33-35]. Chinese patients with type 2 diabetes have a lower BMI when compared to their European diabetic counterpart. They also develop diabetes at a younger age [34]. Lin et al. [36], investigated 4000 asymptomatic Chinese subjects to explore the roles of obesity and dysglycaemia on cardiac structural re-modeling. They found that, in non diabetic subjects fasting blood sugar above 100mg/dl was associated independently with higher left ventricular mass, greater mass-to-volume ratio, more impaired diastolic indices and worse global longitudinal strain. Perhaps the confusion in whether diabetes is an independent risk factor for cardiac dysfunction is due to our definition of diabetes. Insulin resistance was also an independent risk for the above. Lean diabetic subjects had just as much left ventricular re-modeling and diastolic dysfunction as non lean subjects. The authors suggest it is the metabolic disturbance rather than the adiposity per se that causes the cardiac dysfunction.

In 2007 Held et al. [37], examined the association between fasting plasma glucose and risk of hospitalisation for patients who were at high cardiovascular risk and did not have a history of congestive heart failure. Thirty one thousand patients were interrogated in 2 studies. The study found that fasting blood glucose was an independent predictor of hospitalisation for congestive heart failure (CHF) in these high risk patients (age>55 and a history of symptomatic cardiovascular disease or diabetes with evidence of major end-organ damage. The association held both for patients who did not have diabetes and those that had diabetes. In 2012 The Origin Investigators [38] examined whether the long acting insulin Glargine as well as usual care might reduce cardiovascular events. The patients included those with impaired fasting glucose, those with impaired glucose tolerance and those with Type 2 diabetes. The results suggested that the addition of insulin made no difference to outcome [38]. Rodent models of diabetes have suggested that cardiomyopathy in diabetes is associated with fibrosis, mitochondrial dysfunction, oxidative stress, lipotoxicity and metabolic inflexibility [39]. Thus almost the whole metabolic disturbance in diabetes is responsible. Diabetic patients have an increase in LV mass and wall thickness and increased diastolic and systolic dysfunction [40,41]**.** It has been suggested that cardiomyocyte stiffness is promoted by impaired insulin signalling that decreases glucose transporter type 4 (GLUT4) recruitment to the plasma membrane and glucose uptake thus lowering lowering sarcoplasmic reticulum Ca^{2+} pump activity [42,43]. This results in abnormalities in contractile and regulatory protein expression. Abnormal insulin signalling also decreases insulin-stimulated coronary endothelial nitric oxide synthase activity and nitric oxide production increasing cardiomyocyte intracellular Ca^{2+}/Ca sensitization and reducing sarcoplasmic Ca^{2+}uptake [44,45].

Jia et al. [46], have examined the role of mineraloreceptor activation in cardiac dysfunction. Increased activation of the renin -angiotensin-aldosterone system in states of insulin resistance and /or obesity plays an important role in the pathogenesis of cardiac diastolic dysfunction. A good review of the subject has recently been written [44].

Micro RNAs are small non coding molecules that fine tune gene expression via targeting mRNA for translational inhibition [47]. In a review by Rech et al. [48], micro RNAs are discussed in relation to aspects of diastolic dysfunction including inflammation, and macrophage polarisation, microvascular endothelial dysfunction, insulin sensitivity, lipid homeostasis and cardiomyocyte metabolic remodeling, including cardiac fibrosis. The roles of micro RNAs as novel biomarkers in diastolic dysfunction, a difficult condition to diagnose early, are discussed.

In conclusion as there has been a reduction in hospitalisation for acute myocardial ischaemic events there has been an increase in admissions for heart failure in patients with diastolic dysfunction and preserved ejection fraction. This is now a common cause for admission to hospital for diabetic patient. Glycaemia is an independent risk for diastolic dysfunction so it

seems that studies that show the condition is not more common in diabetic patients may have included patients who had raised blood sugars but not in the diabetic range. The association with glycaemia may be an important reason to explain the benefit of good glycaemic control in the prevention of cardiovascular events as shown in type 1 diabetes in the DCCT/EDIC [49] and in UKPDS in Type 2 diabetes [50]. The mechanisms whereby diastolic dysfunction occurs are slowly being unraveled at a molecular level.

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