Review Article

Diabetic Cardiomyopathy: From Pathophysiology to Treatment

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The close relationship between diabetes mellitus and heart failure has been known for many years and includes many mechanisms. In 1881, Leyden first claimed that diabetic cardiomyopathy is a common complication of diabetes and one worthy of attention. In 1888, Mayer reported that diabetes is a disorder of metabolism that can lead to heart disease. Finally, the term "diabetic cardiomyopathy" was introduced by Rubler in 1972, after post mortem studies in diabetic patients with heart failure in whom alcohol, hypertension, coronary disease and other structural heart disease had been ruled out as possible causes.[1]

Epidemiology

Diabetes mellitus has reached an epidemic 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, due to coronary artery disease[3] or associated hypertension, but also because of a direct adverse effect of diabetes mellitus on the heart, the so called diabetic cardiomyopathy. In diabetic patients the prevalence of diabetic cardiomyopathy is 12% and reaches 22% in people over 64 years old.[4]

As was demonstrated in the Framingham Heart Study, diabetes is a strong and independent risk factor for developing heart failure, leading this group of patients to a worse prognosis. The risk of heart failure was 2.4-fold and 5-fold higher in diabetic men and women, respectively, than in non-diabetic subjects. The incidence of heart failure in diabetic patients is still increased even after adjustment for age, hypertension, obesity, coronary artery disease or dyslipidemia.[5] The close correlation between diabetes and heart failure has been demonstrated in many studies. In the United Kingdom Prospective Diabetes Study (UKPDS) an increased prevalence of heart failure was recorded in patients with diabetes mellitus type 2, correlating with levels of glycosylated hemoglobin (HbA1c).[6] The incidence of heart failure is 2.3 cases per 1000 person-years in patients with HbA1c<6% in contrast to 11.9 per 1000 person-years in patients with significantly high HbA1c (>10%). There are identifiable risk factors for developing diabetic cardiomyopathy, such as increased HbA1c,[6] high body mass index, advanced age, use of insulin, proteinuria, the coexistence of coronary artery disease and/or peripheral target organ diseases such as retinopathy and nephropathy.[7,8] In a large case-control study, Bertoni et al[9] tested the hypothesis that diabetes melli-

tus was independently associated with idiopathic cardiomyopathy. After adjusting for age, sex, race, and hypertension, diabetes mellitus was significantly associated with idiopathic cardiomyopathy (relative risk 1.58, 95% CI 1.55–1.62). Similarly in a large population-based cohort study, the Reykjavik Study, Thrainsdottir et al[10] explored the associations between heart failure and abnormal glucose regulation (impaired glucose tolerance or impaired fasting glucose). The odds ratio was 2.8 (95% CI 2.2–3.6) for the association between diabetes mellitus type 2 and heart failure and 1.7 (95% CI 1.4–2.1) for the association between abnormal glucose regulation and heart failure.

Pathophysiology

There are two main types of cardiomyopathy: (1) primary cardiomyopathy, where the cardiac function is aggravated by a defect in the heart itself, and (2) secondary cardiomyopathy, where cardiac performance is affected because of a systemic syndrome.[11] Cardiomyopathy leads to heart failure, which can be either diastolic heart failure, with preserved ejection fraction, or systolic heart failure, with reduced ejection fraction.[12] Diabetes can lead to heart failure, not only by augmenting the impact of classical cardiovascular risk factors (e.g. accelerating the appearance and progression of coronary artery disease through macroangiopathy), but also via a direct deleterious effect on the myocardium *per se*. This condition is known as diabetic cardiomyopathy, defined as the presence of myocardial involvement in patients with diabetes, characterized by dilatation and hypertrophy of the left ventricle, with the concomitant appearance of diastolic and/or systolic dysfunction, and its presence is independent of the coexistence of ischemic or hypertensive or valvular heart disease.[13,14] Myocardial fibrosis and myocyte hypertrophy are the most frequently proposed mechanisms to explain cardiac changes in diabetic cardiomyopathy. Several studies have shown that diabetes causes defects in cellular calcium transport,[15] defects in myocardial contractile proteins,[16] and an increase in collagen formation,[17] which result in anatomic and physiological changes in the myocardium.

Myocardial fibrosis

Myocardial fibrosis, as initially described by Rubler et al and confirmed in histological studies in both experimental subjects and humans,[18-20] is a major consequence of the adverse effects of diabetes mellitus in the heart.[21] Newer echocardiographic techniques should be used in order to evaluate the myocardial collagen content and its pivotal role in cardiac function. Backscatter is an ultrasound tissue characterization technique, based on the measurement of myocardial tissue echoreflectivity, that is related to myocardial collagen content.[22] Di Bello et al[23] demonstrated 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[24] confirmed these results using backscatter in a larger study. Biomarkers of collagen synthesis (procollagen type I carboxy-terminal peptide [PICP], aminoterminal propeptide of procollagen type I [PINP], carboxy-terminal propeptide of procollagen type III [PIIICP], aminoterminal propeptide of procollagen type III [PIIINP]), collagen degradation (CITP), markers of extracellular matrix turnover (such as MMP) and their inhibitors (TIMP, tissue inhibitors of MMP), can be used as markers in detecting myocardial fibrosis.[25] Diabetic 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, a correlation was found between PICP and left ventricular (LV) systolic parameters (fractional shortening and midwall fractional shortening). More specifically, in diabetic patients, corrected endocardial ($r=-0.56$) and midwall shortening ($r=-0.38$) was correlated with PICP, whereas the systolic and early diastolic velocities of the mitral annulus were correlated with glutathione peroxidase (both $r=0.44$).[27]

Hypertrophy of myocardial cells

Studies of cardiac tissue from diabetic animals under the electron microscope have shown multiple abnormalities in the structure of myocardial cells: (i) loss of microfibrils; (ii) loss of cell-to-cell connection in the intermediate discs; and (iii) increased lipid deposition in the cytoplasm and loss of components of the endoplasmic reticulum.[28] Furthermore, it has been reported that LV hypertrophy and concentric remodeling are associated with diabetes mellitus, independently of other confounding factors such as age, obesity, and hypertension.[29-32] Additionally the NOMAS Study described diabetes mellitus as an independent determinant of LV mass, in addition to central obesity as assessed by waist circumference.[33] Fischer et al,

working with cardiac tissue samples from patients undergoing coronary artery bypass grafting, demonstrated no differences in LV hypertrophy and fibrosis between diabetic and non-diabetic patients. They pointed out that the only differences observed in cardiac tissue were related to swelling of endothelial cells and basement membrane thickening of capillaries.[34]

Mechanisms of heart failure in diabetes mellitus

Many pathophysiological mechanisms are involved in the stepwise progression from diabetes mellitus to heart failure. These include direct myocardial injury (e.g. in myocardial ischemia or cardiomyopathy), volume overload (e.g. in aortic valve insufficiency), and pressure overload (e.g. in arterial hypertension). Diabetes not only intensifies the process of atherosclerosis in epicardial coronary arteries, but also promotes the appearance of structural and functional disorders in smaller vessels, resulting in an increased ischemic burden for the myocardium. Furthermore, diabetic cardiomyopathy aggravates hypertension, resulting in increased afterload and pressure overload, and, by contributing to the occurrence of renal failure (diabetic nephropathy), it leads to fluid retention and eventually volume overload.[35-37] From the pathophysiological point of view, in diabetes, because of the lack of insulin or because of insulin resistance in the tissues, the body does not use glucose but instead uses fatty acids as fuel. Although the heart tissue of normoglycemic people prefers free fatty acids as fuel rather than glucose, in diabetic patients this phenomenon is accentuated even further. On the other hand, myocardial cells of normoglycemic patients with heart failure or patients who have suffered a myocardial infarction use glucose as an energy source rather than fatty acids. It seems that in this case glucose exerts a protective role against ischemia.[38,39] The almost exclusive use of fatty acids in diabetes patients leads to their accumulation into the heart muscle, which is followed by the appearance of lipotoxicity. Of particular note is palmitic acid, the accumulation of which influences myocardial contractility and also induces apoptosis of myocardial cells. It has been found that persistent hyperglycemia in the myocardium of diabetic rats stimulates the expression of muscle carnitine palmitoyltransferase enzyme 1.[40] On the other hand, the main feature of diabetes, hyperglycemia, can cause damage to the myocardium via modified proteins (advanced glycation end products, AGEs) and free oxygen radicals (ROS-reactive oxygen species). The AGEs, for example, produced by glycation of collagen lead to its accumulation in the extracellular matrix and eventually in fibrosis of the heart, resulting in diastolic dysfunction. Furthermore, soluble AGEs connected in related receptors (RAGEs), trigger NADPH oxidase, leading to the production of peroxide and ultimately of free oxygen radicals. These in turn cause direct damage to myocyte DNA.[41]

Systolic dysfunction in diabetic cardiomyopathy

Novel echocardiographic techniques, such as tissue Doppler imaging (TDI) and speckle tracking imaging (STI), can be used to detect early subclinical impairment of LV or right ventricular (RV) function in asymptomatic diabetic patients without overt heart disease. Longitudinal dysfunction was demonstrated in many studies using both TDI and STI.[42-49] Several authors demonstrated that longitudinal strain decrease was correlated with diabetes imbalance (glycated hemoglobin) or microvascular complications (microalbuminuria).[50] However, longitudinal alteration is independently associated with diabetes mellitus, regardless of LV hypertrophy or other conventional risk factors. On the other hand radial systolic function has been less investigated, and with conflicting results.[43-45] The initial studies suggested that radial function was increased or preserved to compensate for alterations in longitudinal function. However, most of these studies were based on TDI and its derived velocity and strain rate measurements, which depend on Doppler angle. STI as an angle-independent method could allow a more robust and extensive evaluation of radial function in diabetic as well as in non-diabetic patients.[51]

Left ventricular diastolic dysfunction in diabetic cardiomyopathy

LV diastolic dysfunction, as evaluated from the transmitral LV filling pattern (i.e. abnormal relaxation and/or pseudonormal filling), was observed in 47-75% of asymptomatic normotensive patients with well-controlled diabetes mellitus type 2.[52-54] TDI, as a more sensitive technique for the detection of LV dysfunction, enables the measurement of myocardial tissue velocities in the longitudinal direction, and the peak early diastolic myocardial velocity (e´) reflects the global LV diastolic function. Studies by Kosmala and Di Bonito[55,56] reported that e´

was significantly lower in diabetic patients without hypertension than in normal subjects. Additionally, Boyer et al[53] found that TDI revealed LV diastolic dysfunction in 63% of patients with asymptomatic diabetes mellitus type 2, while conventional Doppler echocardiography was abnormal in only 46% of the subjects. Diastolic variables are related to prognosis in diabetic patients without patent heart disease.[57-59] A study by From et al[56] 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, and left atrial volume.

The right ventricle

It is known that dysfunction of the RV is associated with a worse prognosis in a variety of cardiovascular diseases, including acute myocardial infarction and heart failure. Although most investigators studied the effect of diabetes on the functionality and geometry of the LV, there are also scanty data indicating that diabetes is equally detrimental for the RV. We can assume that in patients with diabetic cardiomyopathy the RV is influenced by both the LV, via a biventricular interaction mechanism, and the diabetes mellitus *per se*. Interestingly, it has been demonstrated that in diabetic patients both the systolic and diastolic function of the RV are affected.[60] In addition, van den Brom et al have shown that in diabetic mice the changes caused by diabetes in the functionality of the RV are in line with those observed in the LV, but the changes in geometry and remodeling are not similar. More specifically, LV changes are characterized by hypertrophy of myocardial cells without dilation, while the opposite was observed in the RV.[61] These interesting findings have also been reported by other investigators.[62]

Clinical presentation and diagnostic approach

In the early stages of diabetic cardiomyopathy the patients are usually asymptomatic. In advanced stages of diabetic cardiomyopathy overt heart failure occurs. Patients develop symptoms due to forward heart failure (weakness, fatigue, angina, syncope) and backward heart failure (dyspnea, raised jugular vein pressure, lower extremity edema, hepatomegaly).[63] Interstitial and perivascular fibrosis is a histological hallmark of diabetic cardiomyopathy, and the extent of fibrosis correlates with heart weight. In addition to the increase in collagen deposition, cross-linking of collagen fibers may be increased by diabetes, contributing to a reduction in ventricular compliance.[64-66] Interstitial fibrosis in diabetic hearts can be assessed by integrated backscatter (myocardial ultrasound reflectivity) in two-dimensional echocardiography and by late gadolinium (Gd) enhancement in cardiac MRI.[67-69] Diabetes (mostly diabetes mellitus type 2) is associated with LV hypertrophy or concentric LV remodeling (i.e. increased ratio of LV mass to LV end-diastolic volume). This finding was previously observed mostly in females using transthoracic echocardiography. However MRI studies have demonstrated that it is not age- or sex-specific.[70] The most frequent echocardiographic finding in patients with asymptomatic diabetes mellitus is LV diastolic dysfunction with preserved LV ejection fraction. Diastolic dysfunction is also detectable in diabetic hearts without hypertrophy.[71] There is also evidence that diabetic patients are at increased risk of arrhythmias, including sudden cardiac death. The underlying arrhythmogenic mechanisms include imbalance in autonomic tone, silent ischemia, slowed conduction, heterogeneities in atrial and ventricular repolarisation, and the extent of myocardial damage and scar formation.[72] Currently, the best approach to the diagnosis of diabetic cardiomyopathy is detection of functional, structural and metabolic changes in the LV and the exclusion of other heart diseases being responsible for these changes in a diabetic patient: Structural changes include: (i) LV hypertrophy, assessed by 2D echocardiography or cardiac magnetic resonance imaging (CMR); (ii) increased integrated backscatter in the LV (septal and posterior wall); and (iii) late Gd-enhancement of the myocardium in CMR.[73] Functional changes are due to: (i) LV diastolic dysfunction, assessed by pulsed Doppler echocardiography and TDI; (ii) LV systolic dysfunction, demonstrated by TDI/SRI; and (iii) limited systolic and/or diastolic functional reserve, assessed by exercise TDI.[74-78] Finally metabolic changes are primarily associated with: (i) a reduced ratio of cardiac phosphocreatine to adenosine triphosphate; and (ii) elevated myocardial triglyceride content.[79,80] Catheter-based diagnosis of diabetic cardiomyopathy is rarely employed at present, because other more sensitive and specific noninvasive techniques are used instead. Coronary angiography is useful for the diagnosis of coronary artery disease that may coexist with and complicate diabetic cardiomyopathy.

Treatment

The pillars in the treatment of diabetic cardiomyopathy are related to lifestyle changes, the regulation of blood glucose levels, modification of risk factors for cardiovascular disease, and the treatment of heart failure.

Lifestyle

Smoking cessation, healthy eating habits, reduction in body weight and aerobic exercise are the cornerstones in terms of lifestyle change. It has been shown in people with diabetes mellitus type 2 that, following reduction of their body weight and increased aerobic activity, the incidence of diabetic cardiomyopathy decreased significantly.[81-84]

Glycemia and other risk factors

The setting of the level of blood glucose is an important target for the treatment of diabetic cardiomyopathy. Achieving euglycemia reduces the risk of major cardiovascular events, such as myocardial infarction or stroke, and the likelihood of developing diabetic cardiomyopathy.[85] The modern therapeutic arsenal has several effective medications to treat diabetes, such as metformin, sulfonylureas, glitazones, insulin, and some modern drugs, such as GLP1 agonists and antagonists of DPP4. Although these drugs appear effective in treating diabetes in people without concomitant heart failure, in patients with heart failure there are some limitations. The classic example is metformin, which has been previously contraindicated in heart failure because of the risk of lactic acidosis. However in clinical practice and use, it turns out that the risk of lactic acidosis associated with metformin in people with diabetes and heart failure is not so great.[86] Additionally, metformin can upregulate cardiomyocyte autophagy, which plays an important role in the prevention of diabetic cardiomyopathy in animal models.[87] Metformin has also been reported to reduce mortality rates and lower all-cause hospital admissions.[88,89] According to some studies, insulin use was considered to be a risk factor for developing heart failure.[90,91] However, those studies were retrospective and non-randomized. Consequently, it is not possible to determine whether insulin treatment truly increases the risk of heart failure, or identifies a higher-risk diabetic patient. Pioglitazone causes an increase in body weight and fluid retention in 5-10% of patients who use this drug. As a consequence, it might worsen heart failure and increase the number of hospitalizations.[92] There is growing evidence to support the use of incretin-based therapies (GLP1 agonists and antagonists of DPP4) for reducing cardiovascular complications in diabetes. In an animal model of atherosclerosis, GLP-1 significantly reduced plaque burden.[93] Apart from anti-atherogenic effects, the GLP-1 pathway may also have cardioprotective properties.[94,95] Increased activation of the GLP-1 axis can improve weight loss and lipid profile, and can lower blood pressure. Moreover, in a small, non-randomized study, GLP-1 infusion was associated with a significant improvement in ejection fraction in patients who presented with acute myocardial infarction and reduced LV function.[96] Additional data are needed to provide important information about the use of these agents for the prevention and treatment of diabetic cardiovascular complications. One of the most hotly debated clinical questions in diabetes is whether intensive glycemic control is associated with better cardiovascular outcomes, and how low we should go in pursuing glycemic targets. The Diabetes Control and Complication Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS) provided consistent evidence that intensive glycemic control prevents the development and progression of microvascular complications in patients with type 1 or type 2 diabetes.[97] However, the Action to Control Cardiovascular Risk in Diabetes (ACCORD), the Action in Diabetes and Vascular Disease (ADVANCE), and the Veterans' Administration Diabetes (VADT) trials revealed no significant effect of intensive glycemic control on mortality or on amelioration of cardiovascular events.[98] The 2013 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases consider tight glycemic control (HbA1c<7%) as a class I indication to decrease microvascular complications and class IIa for the prevention of cardiovascular disease.[99,100]

Heart failure treatment

According to the 2013 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases, three neurohormonal antagonists – an angiotensin-converting enzyme inhibitor (ACE-I) or angiotensin receptor blocker (ARB), a beta-blocker, and a mineralocorticoid receptor antagonist (MRA) – are the most important pharmacological agents for the treatment of

all patients with heart failure and reduced LV ejection fraction, including those with diabetes mellitus. They are usually combined with a diuretic for relieving congestion and may also be supplemented by ivabradine.

Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers

An ACE-I is indicated in diabetes mellitus type 2 and heart failure, since it improves symptoms and reduces mortality.[101-104] The beneficial effects of ARBs are equivalent to those of ACE-I, according to subgroup analyses of clinical trials, and therefore an ARB can be used as an alternative in ACE-I-intolerant patients.[105] When ACE-I and ARBs are used in patients with diabetes mellitus, monitoring of kidney function and potassium is mandatory ,since nephropathy is a frequent occurrence.

Beta-blockers

Beta-blockers are the standard of care in patients with systolic heart failure.[106,107] A subgroup analysis of the MERIT-HF trial showed that beta-blockers reduce mortality and hospital admissions and improve symptoms, without significant differences between diabetes mellitus type 2 and non-diabetic patients.[108] Beta-blockers recommended in heart failure and diabetes mellitus type 2 are metoprolol succinate in the slow release form (MERIT-HF), bisoprolol (Cardiac Insufficiency Bisoprolol Study [CIBIS II]), and carvedilol (Carvedilol Prospective Randomized Cumulative Survival [COPERNICUS] and Carvedilol Or Metoprolol European Trial [COMET]).[109-112] Adverse effects of beta-blockers in patients with diabetes mellitus type 2 and heart failure include: a) hypoglycemia, especially with non cardioselective regimens, and b) negative metabolic effects (hypoglycemia, dyslipidemia and decreased insulin sensitivity).[113,114]

Mineralocorticoid receptor antagonists

An MRA is recommended for all patients with persisting symptoms (New York Heart Association Class II-IV) and an LV ejection fraction ≤35%, despite treatment with an ACE-I (or, if not tolerated, an ARB) and a beta-blocker, to reduce the risk of heart failure hospitalization and premature death (Class IA).[98] The benefit of spironolactone[115] and eplerenone[116] on mortality did not differ between patients with and without diabetes mellitus type 2 and heart failure. Monitoring of kidney function and potassium is mandatory, because of the increased risk of nephropathy in patients with diabetes mellitus.

Diuretics

These drugs are useful for the relief of dyspnea and edema in heart failure with fluid retention, irrespective of the ejection fraction, although there is no evidence of a reduction in mortality or morbidity. Loop diuretics are recommended, rather than thiazides, because of their better glycemic profile.

Ivabradine

The SHIFT trial, involving 6558 patients with heart failure, in sinus rhythm and with heart rate ≥70 bpm (3241 on ivabradine; 30% with diabetes mellitus type 2), demonstrated that ivabradine significantly reduced cardiovascular deaths and hospital admissions for worsening heart failure. The beneficial difference was similar in a pre-specified subgroup analysis of patients with and without diabetes mellitus.[117]

Finally, the presence of diabetes mellitus is not a contraindication for cardiac resynchronization therapy and/or cardiac transplantation in patients with advanced systolic heart failure.

Heart failure with preserved LV ejection fraction is a primary phenotype in diabetes, and therapy to improve the prognosis of this type of heart failure is in general still under intensive investigation.[118]

Conclusions

Diabetes mellitus, a worldwide epidemic disease, affects the heart not only through the intensification of the classic predisposing factors for the development of heart failure, but also through the direct involvement of the myocardial tissue. This entity is called diabetic cardiomyopathy. Newer imaging techniques offer significant information leading to the diagnosis of diabetic cardiomyopathy. Among these, echocardiography should be the main modality involved in the diagnosis and follow up of this entity. Treatment of diabetic cardiomyopathy is based on the general therapeutic rules of heart failure and no specifications have yet been addressed for this entity. Therefore, more studies are required to improve our knowledge of this complex syndrome.

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