Recent advances in the diagnosis and treatment of diabetic cardiomyopathy

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Introduction

Cardiovascular disease is the major cause of morbidity and mortality in patients with diabetes. While it was once thought that ischemic heart disease was responsible for most of these adverse effects, recent data suggest that one of the major adverse complications of diabetes is the development of a specific diabetic cardiomyopathy, characterized by both diastolic and systolic left ventricular dysfunction. Indeed, a bulk of epidemiological, anatomical, experimental animal and human studies indicate the existence of a specific diabetic myocardial disease[1], independent of coronary atherosclerosis. The risk of heart failure is grossly increased in diabetic patients[2], as already evidenced by the Framingham Heart Study[3]. In this study, diabetic male patients had more than twice the incidence rate of heart failure compared to non-diabetic cohorts, while diabetic women showed a 5-fold increased risk. Thus, diabetes mellitus is closely linked to heart failure.

The purpose of the present article is to review the main epidemiologic, prognostic and therapeutic knowledge related to heart failure and diabetes.

Anatomic and functional changes

Several studies have been dedicated to the evaluation of morphological changes in the diabetic heart[4]. Anatomic studies have shown that diabetic cardiomyopathy is mainly characterized by alterations in the microvasculature and myocardial interstitium[5,6]. In the initial stages of the disease, interstitial changes with preserved myocytes and microvascular morphology may predominate and cause the observed reduction in myocardial compliance[7]. With disease progression, salient findings include left ventricular hypertrophy with perivascular, interstitial and replacement fibrosis, and accumulation of periodic acid-Shiff (PAS)-positive material. Arteriolar or capillary involvement typical of diabetic microangiopathy, including increased thickening of myocardial capillary-basement membrane and microaneurysms occurs later in association with more severe myocardial dysfunction[8]. These lesions are not characteristic for diabetes only and appear to be synergistic with structural changes usually observed in arterial hypertension. This fact might be particularly relevant in the light of the positive effects of antihypertensive therapy in diabetic patients observed in the UKPDS[9] and HOT[10] studies.

The above described pathological alterations are associated with a wide range of myocardial dysfunction states, ranging from asymptomatic diastolic dysfunction to overt systolic heart failure. Diminished left ventricular compliance in the presence of normal systolic function is usually the initial step[11,12]. Diastolic abnormalities occur in 27 to 69% of asymptomatic diabetic patients[11,13,14] and may often predict subsequent progression towards the development of frank heart failure[11]. Although diastolic abnormalities have been shown to occur early in the course of diabetes even in the presence of only mild microvascular complications[11,14,15], small vessel coronary disease remains the culprit factor in the pathogenesis of diabetic cardiomyopathy. Interestingly, the combination of diastolic dysfunction[16] and alterations of glucose metabolism[17,18] is also observed in patients with both the metabolic and cardiac syn-

drome X[19] where, again, microvascular disease is likely to play a major role[20].

Even in the absence of frank systolic dysfunction in resting conditions, several studies have shown a lower ejection fraction in response to dynamic exercise[21-23], suggesting a decreased functional reserve in many asymptomatic patients with diabetes. However, even subclinical cardiomyopathy with reduced functional reserve may become clinically important in the context of uncontrolled arterial hypertension and/or the presence of myocardial ischemia. Indeed, diabetic patients experiencing myocardial infarction have a poorer prognosis compared to non-diabetics[24], although infarct size is not larger[25].

Pathophysiology

The pathophysiology of diabetic cardiomyopathy remains largely unknown and several working hypotheses have been investigated. Contributing to its development is a shift in myosine isoenzyme content in favor of the least active V3 form[26]. Calcium homeostasis also appears defective. While calcium transport by the sarcolemmal and sarcoplasmic reticular calcium pumps are minimally affected by diabetes, significant impairment occurs in $Na(^{+})$-Ca^{2+} exchanger activity. This defect limits the ability of the diabetic heart to extrude calcium, contributing to an elevation in $(Ca^{2+})_i$. A decrease in Na^{+}, K^{+}-ATPase activity, which is known to increase $(Ca^{2+})_i$ secondary to a rise in $(Na^{+})_i$, may also promote the accumulation of calcium by the diabetic cell[26]. It is very likely that these defects are related to aberrations of glucose and/or lipid metabolism which involve membrane changes, such as phosphatidylethanolamine N-methylation and protein phosphorylation which, in turn, determine myocyte metabolic dysfunction.

Adverse cardiac effects of diabetes could also be due to the following events. Carbohydrate and lipid metabolism alterations consequent to diabetes mellitus are closely linked to the accumulation of various acylcarnitine and coenzyme derivatives. Abnormally high amounts of metabolic intermediates could cause disturbances in calcium homeostasis which, in the long term, can eventually lead to cardiac dysfunction[27]. In this context, lowering raised plasma triglycerides and free fatty acid levels could therefore decrease the heart's reliance on fatty acids and overcome the fatty acid inhibition of myocardial glucose utilization. In fact, increased levels of citrate, produced by free fatty acid oxidation, inhibit phosphofructokinase, leading to decreased glycolysis and promoting glycogen synthesis. Impaired glucose oxidation also leads to lactic acid accumulation which further promotes the degradation of free fatty acids.

Finally, reduced myocardial blood flow has been clearly related to diabetes mellitus[28], independently of frank epicardial coronary disease and linked to impaired endothelial function[29-31]. Acute hyperglycemia may further impair endothelial-derived vasodilation[32]. In fact, the inability to increase myocardial blood flow appears independently related to long-term blood glucose control[33], indicating that hyperglycemia by itself is of considerable importance for the impaired vascular function. Hyperinsulinemia, by increasing the production of endothelial factors such as endothelins[34], will also probably adversely affect the evolution of cardiovascular disease. In the long term, impaired coronary flow reserve, in the presence of the above described metabolic alterations, might well determine and aggravate a cardiomyopathic process.

In summary, the pathophysiological mechanisms at the base of diabetic cardiomyopathy are likely to be multifactorial, including metabolic and vascular components. This indicates that strict glycemic control and increased free fatty acid oxidation are likely to be beneficial.

Diagnosis

Clinical and instrumental procedures for the diagnosis of diabetic cardiomyopathy do not differ from those adopted for the diagnosis of other forms of cardiomyopathies. Routine electrocardiography and, when necessary, echocardiography remain the gold standard tools. Considering the high prevalence of cardiovascular complications, diabetic patients are regularly prescribed cardiac screening tests that will eventually unmask concomitant cardiac involvement. Nevertheless, in recent years additional tests have been proposed in order to improve the diagnostic accuracy of routine cardiac testing and to detect early diabetic cardiomyopathy. Among the others, tests aimed at evaluating whether sympathetic neuropathy, as assessed by iodine-123-metaiodobenzylguanidine myocardial scintigraphy, could predict subsequent cardiac involvement in asymptomatic patients are still under investigation[35,36].

New echocardiographic methods have also been implemented, such as echocardiographic myocardial texture analysis[37] and ultrasonic myocardial videodensitometric analysis[38]. Indeed, abnormally increased myocardial echodensity, possibly related to collagen deposition, can be detected in asymptomatic diabetic patients with normal rest function. Theoretically, this finding might be considered a very early preclinical alteration potentially related to subsequent development of diabetic cardiomyopathy.

Vectorcardiography has also been shown to potentially predict the occurrence of diabetic cardiomyopathy[39] and, finally, combined myocardial blood flow and glucose metabolism assessment by positron emission tomography has been proposed as a valuable test[40]. The introduction of genetic diagnosis in the near future will

certainly provide the definitive answer to the problem of early detection of diabetic cardiomyopathy[41]. However, despite promising animal studies[42], a specific diagnostic test applicable to humans has yet to be defined.

Therapy

A meticulous metabolic control in diabetic patients will definitely delay the occurrence of cardiovascular complications and improve the prognosis once they have occurred. The specific cardiological therapeutic approach to diabetic cardiomyopathy does not significantly differ from that adopted for other forms of cardiomyopathies. The established use of ACE-inhibitors and beta-blockers in patients with heart failure also applies to diabetic patients. Recent data suggest that the beneficial effects of ACE-inhibition in heart failure patients are even greater in diabetic people[43-45]. The observed super benefits of ACE-inhibitor therapy in diabetic patients are likely due to a variety of mechanisms, since they are greater than those attributable to the decrease in blood pressure[46] and are probably related to specific vasculoprotective and renoprotective effects of ACE-inhibition, mediated by a decrease in angiotensin 2 levels and an increase in bradykinins[47].

Diabetic patients have been traditionally considered less suitable than non diabetic patients for beta-blocker therapy, because of the risk of worsened glucose and lipid metabolism and weakened reaction to potential hypoglycemia. Indeed, classical beta-1 selective beta-blockers reduce insulin sensitivity and impair lipid metabolism. These unfavorable effects are overcome by the introduction of beta-blockers with alpha-1 blocking properties, which have been shown to improve insulin sensitivity and glucose metabolism and should therefore be suitable for diabetic patients[48-50]. Therefore, in the light of the most recent trials of vasodilating beta-blockers in heart failure[51,52], their use in diabetic patients is advocated. Nevertheless, prospective stratification of diabetic patients in large clinical trials would produce important insight into the specific value of beta-blockade in this group of heart failure patients[53].

Finally, recent studies show that patients with advanced ischemic heart failure may benefit from treatment with trimetazidine, a piperazine derivative with fatty acid inhibition properties that is at present employed for the treatment of angina pectoris[54]. These ancillary properties of the molecule have been incidentally observed to be mainly operative in patients who, apart from ischemic cardiomyopathy, are also diabetic. The mechanism of action is related to the property of trimetazidine to facilitate myocardial utilization of glucose instead of free fatty acids which, in the context of malfunctioning myocardial cells, appear to be deleterious. Studies employing ranolazine, a similar drug[55], have come to the same conclusions[56]. Interestingly, compounds that stimulate pyruvate dehydrogenase activity thereby facilitating glucose oxidation and inhibiting free fatty acid oxidation, such as dichloroacetate, have been shown to improve left ventricular function in heart failure patients[57]. Further studies are in progress and, if the preliminary results will be confirmed, partial fatty acid inhibitors will open a new therapeutic strategy in the treatment of diabetic cardiomyopathy.

Conclusions

Diabetes mellitus is becoming progressively common. Most diabetic patients will develop cardiovascular complications, of whom diabetic cardiomyopathy is one of the most frequent and insidious. The early detection of cardiomyopathy in diabetic patients should be actively sought by both cardiologists and diabetologists, aware of its high frequency rate. Apart from meticulous metabolic control of diabetes, cardiomyopathy should be aggressively treated with those drugs at present effectively employed for the treatment of heart failure. Future studies will indicate whether drugs directly affecting myocardial cell metabolism will have any role in the management of diabetic cardiomyopathy.

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