DIABETIC CARDIOMYOPATHY- A DISTINCT CLINICAL ENTITY?

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Abstract: *Cardiovascular disease causes 60% of mortality in diabetics, especially due to heart failure. Diabetes mellitus is an independent risk factor for heart failure. The term "diabetic cardiomyopathy" was first used by Rubler and col. in 1972 and it suggests the direct injury of the myocardium caused by the presence of diabetes. This fact was initially controversial, because systolic and diastolic dysfunction may be due to coronary atherosclerosis, diabetic microangiopathy or to hypertension. The existence of diabetic cardiomyopathy has been confirmed lately by epidemiological, clinical and laboratory studies. Its understanding will allow a better therapeutic management in the future.*

Cuvinte cheie: *diabet zaharat, cardiomiopatie, disfunctie diastolica*

Rezumat: *Patologia cardiovasculară determină 60% din decesele anuale ale diabeticilor, predominant prin insuficienţă cardiacă. Diabetul zaharat este un factor de risc independent pentru insuficienţa cardiacă.Termenul de cardiomiopatie diabetică a fost folosit pentru prima dată în 1972, de catre Rubler şi col. şi sugerează afectarea directă a miocardului prin prezenţa diabetului zaharat, fapt iniţial controversat, deoarece disfuncţia sistolică si diastolică pot fi datorate aterosclerozei coronariene si microangiopatiei diabetice sau hipertensiunii arteriale. Existenţa cardiomiopatiei diabetice a fost demonstrată in ultimii ani prin studii epidemiologice, clinice şi de laborator. Înţelegerea ei va permite in viitor strategii terapeutice superioare.*

The epidemic proportions of diabetes mellitus and the fact that 60% of mortality in diabetics is due to cardiovascular disease, mainly to heart failure (2), becoming an important problem of public health, have brought about the necessity to perform ethiopathogenic studies in this field.(1) Diabetes mellitus is a risk factor for atherosclerosis and its complications, but it is less known as an independent risk factor for heart failure.(2) The term "diabetic cardiomyopathy" was first used by Rubler and col. who described four diabetic patients with heart failure, but without evidence of coronary artery disease, systemic hypertension, or valvular or congenital heart disease. Initially, there was controversy, but, in time, epidemiological, clinical and laboratory evidence came up to sustain this distinct entity and to reveal the underlying biochemical and pathophysiological mechanisms.(1) Although diabetics are at high risk for structural and functional cardiac alterations due to vascular complications, the concept of "diabetic cardiomyopathy" suggests direct myocardial lesions. This is why patients with hypertension and coronary artery disease may have also specific cardiomyopathy with synergic effects.(8) The development of diabetic cardiomyopathy is probably multifactorial.

Metabolic changes

The pathogenesis of diabetic cardiomyopathy starts from the fact that hyperglycaemia, hyperlypidaemia and hyperinsulinemia determine alterations of the transcription factors and changes in gene expression, in using myocardial substrates, in myocyte growth, endothelial function and myocardial compliance. On animals, it was shown that hyperglycaemia and reduction of glucose oxidation determined by the high levels of free fatty acids correlate with systolic and diastolic dysfunction.(7)

Diabetic cardiomyocytes show a significant reduction in the use of myocardial glucose reserve, leading finally to the reduction of ATP availability. The slow rate of glucose transportation across the sarcolemma is probably due to the depletion of glucose transporters 1 and 4, which can be adjusted by insulin therapy.(5)

Hyperglycaemia may produce an excessive formation of advanced glycation end-products and free oxygen radicals with NO deactivation, collagen deposition and fibrosis.

Alterations in fatty acid metabolism due to insulin resistance determine a rise in free fatty acid levels, the impairment of glucose oxidation, alteration of excitation-contraction coupling and the reduction of ATP availability, unbalanced by high mitochondrial ATP production. The reduction of cytosolic ATP leads to the reduction in calcium sequestration by sarcoplasmic reticulum and to impaired relaxation.(11) In addition, the abnormal high oxygen quantity, associated with increased fatty acid metabolism cause intracellular accumulation of potentially toxic intermediates.(3) A relative carntine deficiency is present, common in all diabetics. All metabolic changes mentioned are reversible with a better metabolic control.(5)

Insulin resistance may precede with a decade or more the occurrence of diabetes mellitus and is correlated with the compensatory increase in plasma insulin level, in order to maintain the glycaemic balance. Hyperinsulinaemia causes myocardial and vascular hypertrophy, sodium retention, leading to cardiac decompensation, through volume expansion.

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Hyperinsulinaemia also leads to sympathetic nervous system activation, enhanced response to angiotensin II and its stimulating effect on myocyte growth and collagen production.(3) The role of Renin-Angiotensin-Aldosterone (RAAS) activation is important for the development of diabetic cardiomyopathy. It correlates with the enhancement of oxidative destruction and apoptosis and myocardial and endothelial cell destruction.(11)

Abnormal myocardial metabolism in diabetes causes an excessive production of toxic molecules (long chain acylcarnitines, free radicals), leading to alterations in regulatory and contractile protein function and to the impairment of calcium sensitivity, associated with the shift of heavy chains from V1 to V3 myosin, decrease of SERCA 2a (the sarcoplasmic raeticulum ATP-ase), with ventricular function alteration. It was demonstrated on the diabetic heart that the change in myosin isoenzyme and regulatory protein expression, with myofibrillar remodelling, strongly correlates to the diastolic dysfunction.(5)

Serum copper rises frequently in diabetic patients, the highest values being seen in those with microvascular complications and hypertension. Hyperglycaemia may affect copper binding to caeruloplasmin and albumin with the increase of copper in the extracellular matrix. Also, glycated proteins may have an enhanced affinity for copper. This is why, the rise in extracellular matrix copper might activate the oxydo-reduction systems, rising free radical production and increasing the oxidative stress and fibrosis.(5)

During ischemic events, the adequate response to hypoxia is essential for the protection against myocardial lesions. The hypoxic stimulus is mainly mediated by HIF-1 (hypoxia inducible factor-1), a transcription regulating complex and vascular endothelial growth factor (VEGF). VEGF has a low concentration in diabetic rat myocardium with insulin resistance.(6)

Structural changes

The STRONG Heart Study has shown that diabetics, in comparison with nondiabetics, have a greater left ventricular mass, a greater thickness of the walls and a greater stiffness of arteries, all independent of body mass index and arterial pressure.(2) The Framingham Study showed that ventricular hypertrophy is greater in diabetic women and it is proportional to the degree of glucose intolerance and obesity. Concentric remodelling or growing thickness of the ventricular walls without ventricular hypertrophy is also a feature of the diabetic heart, although it seems that it does not cause diastolic or systolic dysfunction when isolated

Myocardial fibrosis and hypertrophy of myocytes are the mechanisms for pathologic changes in diabetic cardiomyopathy. Collagen deposition in the diabetic myocardium may partially be due to the impairment of collagen destruction, because of collagen lysin residue glycation.(8) Hyperglycaemia may cause oxygen and nitrogen reactive species, enhancing the oxidative stress, causing abnormal genetic expression and apoptosis activation. This process goes together with p53 glycation, causing an enhancement of angiotensin II synthesis, with dose-dependent effects on collagen synthesis. In addition, chronic metabolic changes of diabetes mellitus (postprandial hyperglycaemia, hyperinsulinemia, insulin resistance) lead to alterations of endotelin-1 and its receptors, insulin-like growth factor-I reduction and to the increase of beta1transforming growth factor production, promoting angiotensin II activity and more myocardial collagen contents.(3,12)

Studies using endomyocardial biopsy proved the correlation between the histological and clinical aspects in diabetes mellitus, with more pronounced myocardial changes in the symptomatic patients with cardiomegaly. The role of fibrosis in the development of myocardial dysfunction is sustained by the studies that demonstrate myocardial fibrosis regression after short term treatment with pirfenidone and spironolactone.(9) In the early stages of diabetes, structural changes are usually minimal and may be reversible, or partially reversible. Along with the progression of diabetes, collagen accumulation becomes marked and may play a major part in the development of the diastolic dysfunction.(4)

Vascular changes

Various studies have shown that in the patients with diffuse coronary stenosis, without significant focal stenosis, the diffuse process may lead to an important and continuous reduction of pressure along epicardial coronary arteries, that means a functional equivalent of stenosis. The coronary flow reserve is diminished in the diabetic patients even in the absence of significant coronary stenosis.(8) Hyperglycaemia causes a reduction of the nitric oxide production; it enhances vasoconstrictor prostaglandin production, glycated proteins, endothelial adhesion molecules and vascular and Platelet Growth Factors, all enhancing the vascular tone and permeability. Microangiopathic changes include the thickening of the basement membrane, capillary microaneurysms and the reduction of capillary density, focal subendothelial proliferation and interstitial fibrosis, sometimes with the atrophy of the myocytes.(10) Endothelial dysfunction, altered protein synthesis and endothelial adhesion glycoprotein alteration promote the attachment of monocytes, granulocytes and their transendothelial migration, which leads to myocardial and vascular hypertrophy, deficitary formation of collateral flow and enhanced distal atherosclerosis, that may sometimes not be seen on coronary angiography, but that may play an important part in the pathogenesis of diabetic cardiomyopathy.(5)

Cardiac autonomic neuropathy

Autonomic cardiovascular neuropathy results from the changes in the sympathetic innervations, from the pathological adrenergic receptor expression and from changes in myocardial cathecolamine concentration, with resting tachycardia, orthostatic hypotension and silent myocardial infarction.(6)

Sympathetic and vagal dysfunction was incriminated. The greater prevalence of ventricular fibrillation in the diabetic patients is suggestive for a higher sympathetic tone in the diabetic population. On the other hand, diabetic neuropathy may lead to bradycardia and conduction disturbances. An abnormal pressure response in the upright position was significantly correlated with the reduction of the E/A mitral ratio. This ratio showed a marked reduction in the patients with autonomic neuropathy, the correlation being significant.(1)

Cardiac rhythm variability has been used to evaluate the autonomic imbalance especially for the diagnosis of vagal dysfunction. The reduction of vagal function indices were correlated with a higher mortality, immune dysfunction and inflammation. There may be a pathogenic link between dysautonomia and insulin resistance, obesity and hypertension.(6) High sympathetic tone is correlated with the reduction of adiponectin, which is associated with insulin resistance in diabetics and with circadian disruption of the cardiac rhythm.(4)

Studies with metaiodobenzylguanidine marked with I 123 or with hydroxyepinephrine C11 showed an impaired myocarial uptake in 40-50% of the patients indicating the presence of cardiac autonomic dysfunction. It seems to be a regional process, affecting especially the posterior myocardial wall, proximal hyperinnervation complicating distal denervation. Cardiac autonomic dysfunction is associated with

myocardial blood flow disturbances, the regions with sympathetic hyperinnervation having the greatest deficits of vasodilator reserve. The reduction in myocardial perfusion reserve may partially be the cause of an abnormal response to exercise in the early stages of diabetic cardiomyopathy and may explain the diastolic dysfunction. Still, the exact role of diabetic neuropathy in the development of diabetic cardiomyopathy remains unknown.

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