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# Diabetic cardiomyopathy: current views on the diagnosis and treatment

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## Introduction

Nowadays, advances in technology and the associated increase in the standard of living has lead to a decrease in physical activity and the consumption of processed, high salt foods. As a result, there has been an increase of civilization diseases. Morbidity related to obesity, vascular hypertension, coronary artery disease, diabetes mellitus, chronic heart failure and neoplasma has increased in the population.

Type I or type II diabetes mellitus leads to congestive heart failure and inversely, primary heart failure leads to insulin resistance and finally to the development of the type II diabetes mellitus. Diabetes mellitus along with metabolic disorders contribute to the damage of the majority of organs. Dynamic energetic reactions taking place in the myocardium are disordered. The main source of energy for a cardiomyocyte changes from glucose to free fatty acids (FFA). FFAs start a cascade of processes that damage the myocardium. The result is diabetic cardiomyopathy. Diabetic cardiomyopathy, along with hypertension and coronary artery disease constitute a "cardiotoxic triad". All the diseases, independently, influence anatomy, function and biochemistry of cardiomyocytes [1].

Patients with an early diagnosis of diabetes mellitus, as well as of asymptomatic heart failure, adequate control of glycaemia and an early application of pharmacoteraphy can reduce unfavourable cardiac remodeling and decrease the progression of myocardial disorder [1].

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## The definition of diabetic cardiomyopathy

Diabetic cardiomyopathy has been described for the first time 25 years ago [2]. The term "cardiomyopathy" was described as the sum of disorders caused by the influence of diabetes on heart function and structure. Those disorders include: coronary macroangiopathy (double increase in prevalence and progression of coronary arterial atheromatosis), increased prevalence of hypertension, heart microangiopathy (that is degeneration of small coronary arteries and capillaries, caused by accumulation of glycoprodeids in the vessel wall and by proliferation of endothelium). There is also the autonomic heart neuropathy present, as well as metabolic and biochemical disorders in the cardiomyocytes, and myocardial steatosis in uncontrolled diabetes [3–5].

Macroangiopathy that occur in diabetic patients is the structural basis of ischeamic heart disease. Diabetic cardiomyopathy is caused by primary biochemical damage, highly related to diabetes and microangiopathy of myocardial supply vessels.

The concept of diabetic cardiomyopathy includes degenerative myocardial damage, as a result of metabolic changes in cardiomyocytes, and pathology of small vessels [3–5]. Diabetic cardiomyopathy is characterized as a decrease in heart systolic function which leads to congestive heart failure [6].

The coincidence of cardiomyopathy with small vessel disease or cardiovascular neuropathy cannot be excluded. Myocardial metabolic disorders include: changes in energetic pathways of the heart, structural changes of collagen fibers and contractile proteins, as well as vascular disorders that lead to impaired perfusion. The result of the changes mentioned above and increased fibrosis are stiffness and lack of compliance [3, 6].

The symptoms of circulatory failure in diabetic patients may occur either with heart enlargement (the disturbances in blood supply ma be the cause of myogenic heart dilation in diabetes), or without

cardiomegaly, as so called small stiff heart syndrome in diabetes [3–5].

In diabetic patients with type I and II diabetes with accompanying coronary heart disease, with significant myocardial hypertrophy, without arterial hypertension, it often comes to myocardial infarction, with heart failure as a complication. In a small percentage of patients symptoms of cardiac failure may occur without ischaemic heart disease, heart infarction or arterial hypertension.

In both cases, at first it comes to a functional heart dilation with increase in late-diastolic and late-systolic blood volume in the ventricles, and then to myocardial hypertrophy. An obstruction in blood flow through a certain area of coronary arterial supply results in a quick increase in force of contraction in the remaining, adequately supplied areas of heart muscle. In diabetic patients with coronary heart disease and cardiac failure comes to dyssynergy of muscle fibers during heart systole. The effect of this dyssynergy and heart dilation is increased energy use (oxygen) per each heartbeat in correctly supplied heart muscle fibers. When large left ventricular infarcts are present, and also in post-infarction aneurysm, it comes to hypertrophy of the remaining, well supplied areas. During the process of myocardial overgrowth the arteries, arterioles and capillaries dilate. Their walls thicken, and if they are not capable of proportional dilation and increase in function, myocardial hypertrophy may be halted. The occurence of diabetic microangiopathy hampers the growth of coronary capillaries. This results in faster degeneration of the hypertrophied myocardium and in the beginning of heart failure.

The small stiff heart syndrome is a term referring to the failure of a heart that is not enlarged. It may occur in the syndrome of massive atherosclerosis in 2 or 3 coronary arteries in patients after myocardial infarction. Major fibrosis of the heart prevents its dilation. Diastolic heart compliance is also restricted by areas of focal hypertrophy. The changes mentioned above, due to the extent of atheromatosis and its coincidence with small vessel pathology, occur in patients with long-lasting diabetes. Often the first signs of cardiomyopathy are those of heart failure [4, 5].

Heart volume in radiography in those patients is normal. In echocardiography segmental dyskinesis and traits of diastolic left ventricular failure are found. Decreased heart compliance is characteristic. In cardiomyocytes of some patients, besides muscle hypertrophy, increased collagen hyperplasia is found. Fibrosis with focal hypertrophy is the cause of decreased compliance and increased collagen volume in diabetic patients. It is believed that focal ischaemia without preceeding hypertrophy may cause degeneration or atrophy of the myocardium [4, 7].

## Epidemiology

It has been shown in the past few years that heart failure is an individual risk factor in the development of type II diabetes. It was observed in the Italian CAMPANIA study that in the elderly population, in 3-year observation period, diabetes has developed in 29% of patients with diagnosed heart failure, compared to 18% in the control group [8]. It has been proved that heart failure significantly worsens the prognosis of diabetic patients. Diabetic patients are the group of the highest risk of developing chronic heart failure [1].

Epidemiological data from the Framingham study shows, that heart failure is 5 times more common among diabetic women and 2 times more common in diabetic men than it is in non-diabetics of the same age [1, 9].

Yearly incidence of heart failure in diabetic patients is ca. 3.3%. Aronow et al. [10] stated that in 12% of type II diabetic patients heart failure is found. The results of research on diabetes incidence in the population of chronic heart failure patients vary significantly due to type of research, patient's age, progression of disease, and the definition of diabetes [11].

In diabetic population, both type I and II, a decrease in left ventricle was found in ca. 50% of patients. Also in young diabetics the decrease in left ventricular diastolic function was found [12].

According to echocardiography of diabetic patients, there was a constant progression found, from asymptomatic decrease in diastolic function, through symptomatic diastolic function decrease, to significant decrease in ejection fraction [13].

## Etiology

Risk factors of developing diabetes, such as obesity, lack of physical excercise, are also the risk factors of cardiovascular diseases, including heart failure. Moreover, in type II diabetics are other traditional cardiovascular risk factors present: arterial hypertension, coronary atheromatosis, dyslipidemia. Their occurence does not fully explain greater prevalence of heart failure. The reason of this lies in common pathomechanisms on the cellular level, occuring in different phases of glucose intolerance and insulinresistance [14, 15].

## Myocardial energy metabolism in physiology and in diabetes

Physiologically, glucose metabolism plays a significant role in the heart. It is the basis of ionic pump activity, it is responsible for sustaining the cardiomyocyte membrane potential and for quick calcium ion transport between cellular compartments. Glucose oxidation pathways require less oxygen per mole of produced ATP than the free fatty acid pathways (FFA). Consequently, in myocardial ischaemia, pressure overload, the glucose and lactate become the basic energy source, and glucose uptake may increase up to 30 times [16]. FFAs are an energy source, basic membrane compound, mediators of signal transduction (among other the initiators of apoptosis), ligands of nuclear transcription factors (PPAR-$\alpha$).

Complex glucose and FFA metabolism pathways are responsible for ionic pump function and permeability of cellular membranes. Additional pathways related to those transformations influence the activity of cytoskeletal proteins and enzymes and gene expression.

Toxic influence of hyperglycaemia and glycation of heart proteins are, among others, major mechanisms resulting in structural and functional damage of cardiomyocytes [5].

Metabolic factors in diabetic patients have a major influence on the function of the myocardium and the whole circulatory system. In diabetic patients the glucose metabolism in the heart is insufficient, what results in increased energy production from FFA $\beta$-oxidation pathways. Change of the oxidation substrate from glucose to free fatty acids is a major cause of pathology because the FFAs damage the myocardial function.

The levels of insuline, FFAs and glucose are increased in type II diabetics.

It has been proved in experimental research on animal models that the levels of glucose transporter mRNA are decreased, which results in the decrease of protein expression and impaired glucose transport into the cardiomyocytes. Consequently, non-oxidative glycolysis and lactate acidosis increase. Under those circumstances, cellular and intercellular calcium transport is decreased, what causes progression of left ventricular dysfunction, even in the absence of ischaemia. Physiological mechanism of increasing contractile function and lactate uptake under adrenergic stimulation, adequate to increased loading, is not observed in the myocardium of diabetic patients. In the heart of a diabetic patient there is a decrease in the ability to oxidate glucose and lactate, secondary to decreased ability to oxidate pyruvate by the mitochondria [14]. Increased lactate production and overloading of the cardiomiocytes with calcium ions, contribute to cardiomyocyte apoptosis and consequently to impairment of myocardial function [14].

Pyruvate oxidation rate depends on, among others, on the substrate and product levels in the mitochondria. Increased level of acetylcoenzyme A and FFA observed in diabetic patients suppresses pyruvate metabolism through inhibition of pyruvate dehydrogenase, what impairs glucose oxidation [17]. Additionally the level of triglicerole is increased in the myocardium of diabetic patients. Metabolism disturbances in the heart of diabetic patients impair the adaptation to ischaemic or overload condition. At first the heart adapts to altered energetic conditions through increased expression of genes coding proteins that take part in FFA metabolism, what increases the availability of the FFAs and allows use of their energy. However, progression of diabetes and additional damaging factors, such as arterial hypertension lead to failure of adaptive mechanisms. FFA redundance cannot be transported to the mitochondria and be used by the heart, what leads to increase in cytoplasmatic acetylcoenzyme A level. Their utilization is performed through diacylglycerole and ceramide synthesis. Diacylglycerole causes permeability disturbances of cardiomiocyte membrane, through chronic activation of $\beta$-protein kinase C isoforms. This causes the insulin resistance and occurrence of contraction disorders. The expression of C-$\beta$2 protein kinase in the miocardium leads to the development of cardiomyopathy [5].

Both FFA and chronic hyperglicaemia increase the production of free oxygen radicals, the presence of which results in the impairment of cellular metabolism. They impair the function of contractile and enzymatic proteins, as well as of endothelial regulators. It comes to disturbances in ionic channel function, calcium homeostasis, activity of transcription agents that bind to DNA, as well as to the initiation of apoptosis [18]. Additionally, high concentrations of FFAs increase sympathetic activity.

Beta-oxidation of FFAs may be suppressed by glucose. As a result of hyperglicaemia and high FFA concentration it comes to increased deposition of lipids in cardiomyocytes, what results in heart function impairment. In cardiomyocytes of diabetic patients there was an accumulation of intermediate glucose metabolism products found, what is the result of decreased availability of glucokinase and inhibition of phosphofructokinase and pyruvate dehydrogenase activity, due to increased FFA level and intracellular lipids overload.

The glycation of proteins that take part in insuline signal transduction under the conditions of increased glucose concentration induces insuline resistance [11]. Deposition of the so called advanced glycation end-products disturbes the balance between oxidation and reduction in endothelial cells, leading to oxidative stress [14].

Toxic products of FFA metabolism cause decrease of sarcoplasmatic calcium pump, blocking ATP-dependent potassium channel and NaK ATP-asis activity impairment. It comes to impairment of the calcium outflow from the cardiomyocytes during diastole. Decreased Mg inflow and loss of potassium ions is observed [5]. Insulin deficiency impairs NO production, and insulin resistance inhibits vasodilatation caused by NO [5].

Metabolism impairment and insuline resistance occurring in diabetic patients are both cause and result of diabetic cardiomyopathy. It was observed that heart failure may be the cause of insulin resistance that impairs myocardial function [15].

Insulin resistance in primary heart failure develops as a result of epithelial dysfunction and decrease in blood flow in skeletal muscles. Heart failure is a condition decribed as a "storm" of inflammation markers.

Cytokines circulating in the blood of the patients, such as for instance TNF-$\alpha$ contribute to insulin resistance and type II diabetes development [19].

Impairing vascular endothelium function in patients with insulin resistance or with diabetes contributes to repetitive ischaemia and worsening of miocardial function. This process leads to greater vascular permeability, and as a result to interstitial oedema, fibrosing and myocardium dysfunction.

In diabetic patients decreased angiogenesis was observed, which may also cause damage of the miocardium [11, 20].

It comes to destructive changes in interstitial collagen, what is influenced by glication [7]. Increased sympathetic activity, decreased mass of skeletal muscles, fatigue, lower level of physical activity deepen changes in metabolism typical for diabetes, contributing to development of a "vicious circle" and progression of heart failure as well as insulin resistance [11, 21].

## Activation of neurohormonal system

Extension of the ventricles and increase in left ventricular wall tension result in activation of sympathetic system as well as the renin–angiotensin––aldosterone system. Hyperglycaemia has similar influence on neurohormonal system. At first, this condition is an adaptation to altered circumstances, in order to prevent tissue hypoperfusion.

As a result of myocardial hypertrophy and remodeling, the volume and shape of the ventricles change. Then it comes to accelerated apoptosis of the cardiomyocytes. Heart function impairment deepens, resulting in increased neurohormonal activation [11]. With time it comes to breakdown of the compensation mechanism and the development of symptomatic heart failure [19].

It comes to the induction of fetal gene programme and to disturbed signal transduction in $\beta$-adrenergic receptors, what induces carnitine palmitoilotransferase I and increases the use of FFAs in the myocardium.

Overuse of the FFAs causes inhibition of membrane ATP-ase, what increases oxygen requirement, leading to ischaemia, myocardial function impairment and occurence of heart rhythm disturbances. Cardioprotective activity of $\beta$-adrenolytic drugs is based probably, among others, on inhibition of carnitine palmitoilotransferase I activity [11].

## Alterations in gene expression

The hearts of diabetic patients show several similarities to the fetal heart fetal. It is caused by adaptation to hyperglycaemia and the presence of FFA's metabolism products. In the myocardium of diabetic patients it comes to reexpression of genes — the activity of genes characteristic to fetal period increases, what is initially beneficial in terms of sustaining systolic function. The accumulation of intermediate products of glucose metabolism, as a result of dissociation between glycolysis and pyruvate oxidation, in hyperglycaemic conditions result in activation of glucose-related transcription agents. Disturbance in signal transduction in $\beta$-adrenergic receptors also results in altered gene expression.

It comes to $\alpha$-actine gene induction, which is characteristic for skeletal muscles and is not found in healthy heart muscle after birth. In diabetic patients the expression of various myosine chains alters in the myocardium. It comes to lowering of the concentration of the quick isoform of heavy $\alpha$-chains and increase in free fetal $\beta$-isoform. The level of glucose probably influences the regulation of the processes mentioned above [22, 23].

The activity of sarcoplasmatic reticulum $Ca^{2+}$ ATP-ase (that is the sarcoplasmatic calcium pump, an inotropic protein) is decreased. The result of those changes is initially decreased ability to relax and eventually impaired systolic and diastolic function [24].

## Prognosis

Hyperglycaemia and diabetes significantly worsen the prognosis of a patient with chronic heart failure. The Rotterdam study showed that diabetes influences overall mortality in a similar manner as left ventricular dysfunction does [25]. Patients having diabetes coexisting with heart failure secondary to coronary heart disease have a much higher overall mortality [26].

It was observed in the SOLVD and RESOLVD studies that diabetes is an independent mortality risk factor in patients with lower ejection fraction and in patients with heart failure [27, 28]. However in diabetic patients the cardiovascular complications, including heart failure, are the major cause of death, especially in women and in elderly population [14].

## Diagnosis and treatment

The diagnosis of symptomatic heart failure is not very difficult. A detailed anamnesis, physical examination, ECG, RTG and transthoracic echocardiogram evaluation is essential. However, diagnosing an asymptomatic diastolic and/or systolic dysfunction is a real challenge. In this case, determination of NT-proBNP peptide or BNP in patient's blood and detailed echocardiography is useful. A study conducted by Epshteyn et al. [29] showed that in diabetic patients determination of the BNP may reliably confirm or exclude left ventricular dysfunction. BNP concentration, unlike ANP concentration, does not change with glucose concentrations [11].

In the treatment of diabetic patients with coexisting heart failure correct glycaemia control and selection of drugs that do not increase glucose metabolism impairment are essential.

It was proved that better metabolic control in type II diabetes treated with insuline contributes to better left ventricular diastolic function and increase in microvessel perfusion reserve [30]. According to those findings, the loop diuretics are recommended, because thiazides have a disadvantageous influence on glucose metabolism.

A significant decrease in mortality was observed after introducing angiotensin corverting enzyme inhibitors to therapy. Drugs from this group may lower insulin resistance and cause hypoglycaemia as a consequence [31, 32].

In experimental work, use of etomoxir, an FFA $\beta$-oxydation inhibitor, has resulted after 3 months in a signficant increase in left ventricular ejection fraction and maximum ejection volume in physical excercise [33]. The activity of this drug is explained by increasing glucose oxidation and decreasing in SERCA2a expression caused by diabetes and volume overload [33].

Trimethazidine increases glucose use in the heart, inhibiting a key FFA mitochondrial uptake regulatory enzyme, that is carnitine palmitoilotransferase I. In TRIMPOL-1 study a significant increase in physical efficiency was proved [34].

Beta-adrenolytic drugs prevent cardiotoxic sympathetic activation. In diabetic patients a chronic sympathetic activation occurring in heart failure is additionally increased by insulin resistance and hyperinsulinaemia. This results in fetal gene reexpression and myocardial remodeling. Beta-adrenolytic drugs reverse heart remodeling and improve left ventricular systolic function. Moreover, they have beneficial effect on metabolism of the myocardium, they lower FFA use together with increase in glucose oxidation, and significantly reduce risk of death. The results of studies on carvedilol and metoprolol support the use of those drugs in all patients with stable heart failure, if no absolute contraindications are present, especially in diabetic patients [7, 11, 35–37]. However, application of $\beta$-adrenolytic drugs may make it more difficult to diagnose hypoglycaemia. This problem may be rather irrelevant with the 3$^{rd}$ generation drugs. Carvedilol does not influence insulin sensitivity and glucose accessibility. It causes peripheral vessel dilatation, increase HDL cholesterol concentration and lowers triglyceride concentration [38, 39].

## Diabetic *versus* primary cardiomyopathy

An important etiological factor of primary cardiomyopathy is probably the small vessel disease. It is believed that most of the "undefined" cardiomyopathies is a result of inherited tunica media necrosis in the small coronary arteries [4].

In patients with long-lasting diabetes comes to cardiomyopathy which is a result of specific degenerative changes in small coronary arterioles and capillaries, as a result of autonomic heart neuropathy and metabolic-derived myocardial fiber damage. Changes observed in these patients are of mixed character, and are usually a result of both microangiopathy and macroangiopathy. This may result in hampering of heart hypertrophy. As a result it comes to a cardiomyopathy called "small heart syndrome", with decreased diastolic compliance. A second form of diabetic cardiomyopathy is myogenic heart enlargement (cardiomegaly). The mechanisms described above in diabetic patients contribute to greater incidence of chronic congestive heart failure and are also the cause of variable course of diabetic cardiomyopathy [4, 5].

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