Diabetes mellitus and cardiac function

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Abstract
Cardiovascular complications are the most common causes of morbidity and mortality in diabetic patients. Coronary atherosclerosis is enhanced in diabetics, whereas myocardial infarction represents 20% of deaths of diabetic subjects. Furthermore, re-infarction and heart failure are more common in the diabetics. Diabetic cardiomyopathy is characterized by an early diastolic dysfunction and a later systolic one, with intracellular retention of calcium and sodium and loss of potassium. In addition, diabetes mellitus accelerates the development of left ventricular hypertrophy in hypertensive patients and increases cardiovascular mortality and morbidity. Treating the cardiovascular problems in diabetics must be undertaken with caution. Special consideration must be given with respect to the ionic and metabolic changes associated with diabetes. For example, although ACE inhibitors and calcium channel blockers are suitable agents, potassium channel openers cause myocardial preconditioning and decrease the infarct size in animal models, but they inhibit the insulin release after glucose administration in healthy subjects. Furthermore, potassium channel blockers abolish myocardial preconditioning and increase infarct size in animal models, but they protect the heart from the fatal arrhythmias induced by ischemia and reperfusion which may be important in diabetes. For example, diabetic peripheral neuropathy usually presents with silent ischemia and infarction. Mechanistically, parasympathetic cardiac nerve dysfunction, expressed as increased resting heart rate and decreased respiratory variation in heart rate, is more frequent than the sympathetic cardiac nerve dysfunction expressed as a decrease in the heart rate rise during standing. (Mol Cell Biochem 180: 59–64, 1998)

Key words: heart function, metabolic changes in the heart, diabetic cardiomyopathy

Introduction
Diabetes mellitus (DM) is a generalized metabolic disorder characterized by certain abnormalities in carbohydrate, fat, electrolyte and protein metabolism which ultimately lead to several acute and chronic complications. DM is classically classified into Insulin Dependent (IDDM) or (type I) and Non-Insulin dependent (NIDDM) or (type II). Predictors of diverse complications of DM could be listed as follows: the duration of the disease, previous use of insulin (negative correlation), glycemia, alcoholism, smoking habit, and intake of legumes (beans). Peripheral neuropathy, amputations, renal impairment, albuminuria, myocardial infarction, cataract, and amaurosis fugax are strongly associated with the duration of diabetes rather than with the age of the patient or the age at the diagnosis. In contrast, hypertension, and impotence are associated more with the age of the patient [1]. The purpose of this review is to summarize the cardiac complications associated with DM and to indicate means of cardiac protection. Cardiovascular complications are the most common causes of morbidity and mortality in the diabetic patients. The acceleration of atherosclerosis occurs in all types of DM and culminates in such fatal complications as myocardial infarction, stroke and gangrene. Subjects with NIDDM exhibit 3–4 times higher rate of cardiovascular mortality than non-diabetic persons. Various hypothesis have been introduced to explain the relationship between DM and the cardiac diseases, for example, elevation of blood pressure, changes in lipid metabolism, hypo-insulinemia, abnormal hemostasis, and abnormal kidney function [2]. In this review, we will discuss three aspects of cardiac complications in the diabetic patients. These aspects are coronary atherosclerosis, diabetic cardiomyopathy and autonomic neuropathy.

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Coronary atherosclerosis

Many studies demonstrate that the prevalence of coronary artery disease (CAD) is increased among diabetic patients. CAD is the most common cause of death in type II DM, but it also contributes to mortality in type I diabetic patients. The incidence of CAD increases in female patients [3]. Myocardial infarction is the cause of death in about 20% of diabetic patients, with an increased incidence of complications such as congestive heart failure, cardiogenic shock, arrhythmias, and ventricular rupture. Letho et al. [6] reported that the infarct size in patient hearts, measured as maximal levels of serum cardiac enzymes and QRS score, are not significantly different between diabetic and nondiabetic patients. However, post-infarction mortality rate is higher in the diabetic patients because diabetic subjects have increased liability of complications as re-infarction and heart failure. Silent myocardial infarction is a common feature of CAD in diabetics as an indicator of neuropathy [4]. In diabetic patients, the heart shows a decrease in the maximal coronary vasodilator response to papaverine and adenosine therapy. This is accompanied by attenuation of the decreased coronary vascular resistance in response to the increasing myocardial metabolic demands as in the use of isotropic stimulation or rapid atrial pacing. These findings suggest structural and functional abnormalities in the coronary microcirculation in diabetic patients as they are not related to differences in drug therapy, resting hemodynamic or an incidence of hypertension [5].

Ionic hemostasis and ventricular arrhythmias

The ion shift in the form of intra-cellular sodium and calcium retention and potassium loss occurs in the ventricular myocyte in diabetic animals. This ion shift is pronounced when the heart is subjected to ischemia/reperfusion increasing the risk of ventricular tachycardia and fibrillation. These fatal ventricular arrhythmias are accentuated by KATP channel openers and blocked by KATP channel blockers. Glibenclamide is a KATP channel blocker commonly used as an oral hypoglycemic drug in NIDDM. This drug decreases the fatal ventricular arrhythmias mediated by ischemia reperfusion but not the spontaneous arrhythmias [7]. In the ischemic rat heart, the pH rise during reperfusion continues even with the blockade of Na+/H+ exchange by, amiloride. Recovery of pH occurs more rapidly in diabetic hearts receiving HEPES buffered solution than in those receiving bicarbonate buffered solution suggesting that the bicarbonate dependent mechanism of pH regulation may be depressed in diabetes [8]. Reduction of the risk of CAD in diabetics could be achieved mainly by the control of obesity, correction of hypertension, elimination of cigarette smoking and improvement of LDL/HDL cholesterol level. Tight metabolic control and insulin infusion in early post-infarction do not have immediate beneficial effect. However, the long term mortality which is associated with re-infarction and heart failure is decreased with metabolic management [6].

Coronary artery bypass graft (CABG) is usually considered in the management of diabetic patients with CAD. Diabetic CAD patients usually present with an angiographically triple vessel disease with no predominant single vessel affected [9]. The complications during and after CABG operation increase in the diabetic patients, and especially include sternotomy complications, renal insufficiency, and cerebral stroke [10].

Diabetic cardiomyopathy

While it had been thought that atherosclerotic vascular disease was responsible for all the adverse effects of DM on the heart, recent studies support the notion that one of the major adverse complications of DM is the development of diabetic cardiomyopathy. Diabetic cardiomyopathy is characterized by early diastolic dysfunction and late systolic impairment. Contributing to the development of the cardiomyopathy is a shift of myosin isoenzyme content in favor of the least active V1 form. The main ion defect in diabetic cardiomyopathic cell is a defect in the regulation of calcium hemostasis during transport of calcium by the sarcolemma and sarcoplasmic reticulum. Calcium pumps are minimally affected by non-insulin dependent diabetes. Significant impairment occurs in sarcoplasmalum sodium-calcium exchanger activity. This defect limits the ability of the diabetic heart to extrude calcium, contributing to an elevation in intracellular calcium. The decrease in Na+/K+ ATPase activity increases intracellular calcium retention secondary to increased sodium; in addition, calcium influx via the calcium channel is stimulated. Although the molecular mechanisms underlying these abnormalities are presently unknown, the possibility that they may be related to aberrations in glucose and lipid metabolism are considered. Evidence suggests that classical theories of glucose toxicity, such as excessive polyol production or glycosylation appear to be insignificant factors in heart. Also defects in lipid metabolism leading to the accumulation of toxic lipid amphiphiles or tri-acylglycerol appear insignificant. Rather, the major defects seem to involve changes in membrane structure, such as phosphatidyl-ethanolamine N-methylation and protein phosphorylation which can be attributed to the state of insulin resistance [11].

To study the abnormalities in the myocardium energy metabolism in the diabetic animals, by using 13C-NMR spectroscopy, glucose metabolism in the isolated diabetic perfused rat heart was studied. In the control hearts, the labelled form (13C)glucose was incorporated into lactate and