Abnormalities in ATP Production and Utilization in Diabetic Cardiomyopathy

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Abstract For the heart to produce mechanical force, two cellular components are essential: myofibrils, which are responsible for generating contractile activity, and mitochondria, which provide most of the required energy. Diabetic cardiomyopathy is associated with defects in both mitochondria and myofibrils, indicating that changes in energy production and energy utilization are of foremost relevance in the etiology of cardiac dysfunction in chronic diabetes. Several elements including hyperglycemia, hyperlipidemia, and changes in the level of different hormones contribute directly or indirectly to contractile impairment in this multifactorial diabetic disorder. Metabolic imbalance, characterized by excessive fatty acid oxidation, Ca^{2+} overload, and oxidative stress are considered to reduce mitochondrial phosphorylation activity and impair the mitochondrial electron-transport chain in the diabetic heart. These subcellular alterations result in reduced level of adenosine triphosphate (ATP) in the diabetic heart, limiting cardiomyocyte contractile ability. Altered gene expression and excessive proteolytic activity caused by intracellular Ca^{2+} overload and oxidative stress in chronic diabetes promote changes in both composition and structure of myofibrils; this myofibril remodeling, characterized by diminished energy consumption and insensitivity to Ca^{2+}, further impairs heart function in diabetic cardiomyopathy.

Keywords Diabetic cardiomyopathy • Mitochondria • Myofibrils • ATP • Metabolic abnormalities • Ca^{2+} overload • Oxidative stress • Cardiac dysfunction

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1 Introduction

Diabetes mellitus is becoming a more relevant disease, as the global prevalence of diabetes was estimated to be 2.8 % in 2000 and is expected to increase more than 50 % until reaching 4.4 % in 2030 [1]. Diabetes is associated to a wide range of clinical manifestations related to either insulin deficiency in type 1 diabetes or insulin insensitivity in type 2 diabetes [2, 3]. This abnormal metabolic state is mainly characterized by, but not limited to, hyperglycemia (elevated glucose levels). Other hormonal and metabolic abnormalities, especially hyperlipidemia, are known to contribute to diabetes-related cardiovascular complications [4–9]. Although the name diabetes mellitus, in opposition to insipidus, is a remnant of a time when tasting urine was an acceptable medical procedure, the idea of a defective cardiac phenotype as a result of diabetes is a relatively new concept. Although diabetes mortality is primarily attributed to cardiovascular complications [10], the concept of diabetic cardiomyopathy was neglected for a long time, mainly because of the confounding effect of chronic diabetes on heart function by atherosclerosis and hypertension [9, 11]. It was in 1972, with the description of four diabetic patients showing congestive heart failure in the absence of coronary artery atherosclerosis by Rubler et al. [12], that the term diabetic cardiomyopathy was first used. Diabetic cardiomyopathy was defined as a cardiac dysfunction that occurs because of chronic diabetes, independently of coronary artery disease [13]. Patients with diabetes, in the absence of atherosclerosis, were found to suffer from ventricular dysfunction including shortened left ventricular ejection time, longer pre-ejection period, and also elevated end-diastolic pressure [14]. Some epidemiological studies also revealed that diabetes shows increased risk of heart failure even when atherosclerosis and hypertension risks are taken into account [15]. Animal models for diabetes also attest to the harmful effects of diabetes on heart function. Streptozotocin-induced diabetes in rats is associated with reduced heart rate, lower peak ventricular pressure- and also impaired left ventricular contractions and relaxations [16–21]. Further animal studies have also shown that diabetes, in conjunction with hypertension, leads to congestive heart failure [22, 23].

Although the molecular and cellular mechanisms of the cardiac dysfunction in diabetic cardiomyopathy are not completely understood [24], it is clear that an imbalance between energy production, in the form of adenosine triphosphate (ATP), and energy consumption is a key factor that contributes to the development of this pathological disorder [13, 24, 25]. The major players of the high-energy phosphate production and utilization cycle, in the cardiomyocytes, are the mitochondria (MT) and myofibrils (MF), the subcellular components responsible for the phosphorylation of adenosine diphosphate (ADP) into ATP and the hydrolysis of ATP by ATPase activity, respectively. Herein, this review focuses on the mechanisms by which chronic diabetes affects MT and MF functions, and also the consequences of the resulting energetic imbalance on cardiomyocytes and heart function.

2 Defects in Energy Production

In cardiac tissue, as in most tissues, MT are accountable for most of the ATP production, and thus any deterioration of these organelles may lead to a state of energy restriction and consequently of cellular deficiency. In fact, MT are responsible, under normal conditions, for more than 95 % of all myocardial ATP synthesis [26]; cardiomyocytes have a rather limited ATP pool that would be consumed in approximately 10 s without continuous mitochondrial activity [26]. To maintain a stable ATP content, and proper myocardial function, energy consumption and production have to be tightly coupled in the cardiac muscle. Proper MT function is, therefore, essential for cardiac function as MT phosphorylation is commonly compromised in several different types of cardiac disorders [26–28], including diabetic cardiomyopathy [29–31]. MT dysfunction is mainly credited to metabolic alterations in diabetes, resulting in increased free fatty acid (FFA) utilization. Oxidative stress and Ca^{2+} overload are also relevant to the process that leads to MT damage and energy deficiency in the diabetic heart. These events are depicted in Fig. 1.

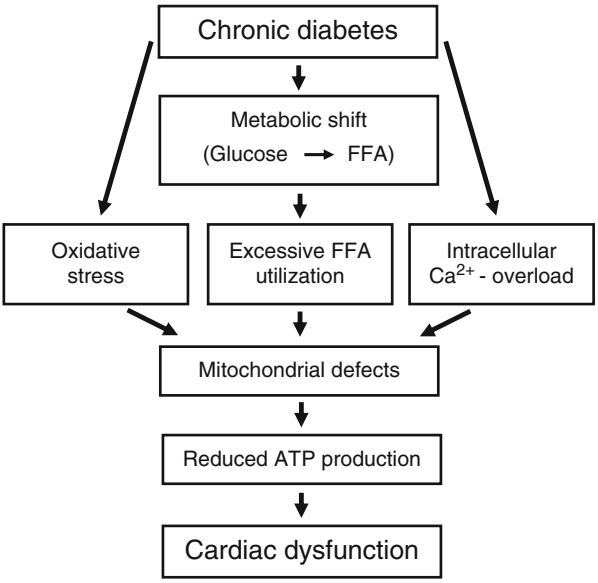

Fig. 1 Mechanisms by which chronic diabetes leads to mitochondrial defect, reduced ATP reserves, and cardiac dysfunction

3 Defects in Energy Utilization

Cardiomyocytes require energy, in the form of ATP, to produce MF contractions and the mechanical force that ultimately allows the heart to pump blood. Because cardiomyocyte contractions are controlled, in both intensity and rhythm, by changes in intracellular Ca^{2+} concentration, a precise MF response to Ca^{2+} is crucial to overall heart performance. MF is the functional unit of the cardiac muscle, being composed mainly of actin and myosin; myosin is the protein that is actively responsible for muscular contractions, as it possesses ATPase activity. MF contractions are regulated by the troponin–tropomyosin complex (TnTm): Ca^{2+} binds to the TnTm complex, which exposes the myosin ATP-binding site, and this allows actin–myosin interactions to occur, resulting in the shortening of the muscle fiber. This contractile process requires energy in the form of ATP and represents about 60–70 % of all ATP consumption of the myocardium under normal conditions [26]. As a matter of fact, diabetic cardiomyopathy is associated with MF abnormalities that result in defects in the energy utilization process [13, 32–34]. Two main factors can be seen promoting cardiac contractile dysfunction: defects in energy utilization and abnormal MF regulation. Several cellular abnormalities involved in defects in energy utilization and regulation of MF in diabetic heart are depicted in Fig. 2.

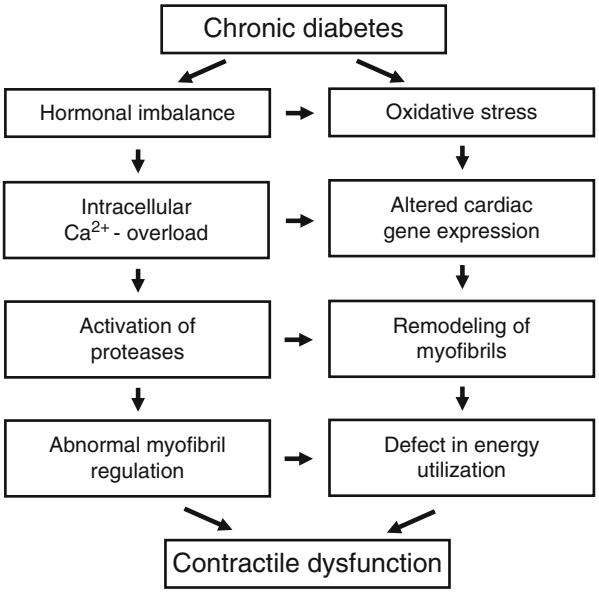

Fig. 2 Role of hormonal imbalance in diabetic cardiomyopathy in promoting myofibrillar dysfunction, as a consequence of oxidative stress, Ca^{2+} overload, and the activation of proteolytic enzymes

Abnormal energy utilization is associated with MF remodeling, a process that is related to changes in gene expression, oxidative stress, intracellular Ca^{2+}, and activation of proteolytic enzymes [13, 21, 32, 34, 35]. Several animal studies have reported decreased MF Ca^{2+}-dependent ATPase activity in chronic diabetes [17, 19, 21, 36, 37], and MF insensibility to Ca^{2+} is most likely involved in diabetic cardiomyopathy [13]. Several factors interfere with myofibril function, involving both functional and regulatory enzymes [36–39]. Chronic diabetes, in animals, is associated with the prevalence of myosin heavy-chain (MHC) isoenzyme β over isoenzyme α [34, 40–48]. This shift in expression of MHC isoforms could explain the depressed ATPase activity in other animals; however, the relevance of this mechanism is uncertain in human hearts, in which the β-isoform is normally predominant over the α isoform [49, 50]. On the other hand, the phosphorylation of the myosin light chain (MLC) by the myosin light-chain kinase (MLCK) is a factor that could explain cardiac dysfunction in human diabetic cardiomyopathy, because MLC phosphorylation is related to increased MF sensitivity to Ca^{2+} [51]. However, MLC, MLCK, and MLC phosphorylation were shown to be significantly reduced in diabetic rat heart homogenate, and these changes were partially reversed by insulin treatment [38]. The activation of proteolytic enzymes, seen in cardiac dysfunction [35, 52–60], can also participate in the development of MF dysfunction. Intracellular Ca^{2+} overload and oxidative stress are related to the activation of proteases [61–63] that would lead to degradation of cardiomyocyte MF proteins in diabetic cardiomyopathy.

Chronic diabetes is also known to affect cardiac function through impaired MF regulation mainly caused by TnTm abnormalities [13]. The TnTm complex is formed by tropomyosin and three subunits of troponin, TnC, TnI, and TnT, that are responsible for Ca^{2+} binding, ATPase inhibition, and myosin binding, respectively. There is evidence that the phosphorylation of TnI and TnT by protein kinase A (PKA) and C (PKC) contribute to myofibrillar insensitivity to Ca^{2+}, leading, in the given order, to reduced ATPase response to Ca^{2+} and reduced myosin–actin interactions [13]. These findings are supported by the fact that impaired actomyosin ATPase activity of diabetic animals could be partially normalized in the presence of TnTm extracted from healthy animals [64].

4 Mechanisms of Alterations in Mitochondria and Myofibrils

The primary energy source of cardiomyocytes are fatty acids, accounting for approximately 60–70 % of the myocardial substrate [65]. The participation of FFA in cardiac muscle energy metabolism is known to be even more expressive in a chronic diabetic state [66, 67]. Although lipids are essential for heart function, from both an energetic and structural point of view, excessive FFA uptake by myocytes is known to have deleterious effects on cardiac function, supporting the concept of ‘lipid paradox’ [65]. Studies conducted with both animal and human tissues have concluded that

sarcolemmal (SL) glucose transporter (GLUT) 1, GLUT4, and sodium–glucose-linked transporter (SLGT) 1 expression is reduced in diabetic hearts [68–76]. In fact, glucose uptake is impaired in diabetic hearts by insulin deficiency or insensitivity [77–79]. The opposite is true for FFA uptake: high plasma levels of FFA not only increase cardiomyocyte FFA uptake but also depress glucose utilization by the diabetic heart [26, 28, 80]. Increased MT fatty acid oxidation, in chronic diabetes, is credited to the upregulation of the perioxisome proliferator-activated receptor α [71, 81–84]. Such an elevation in the rate of fatty acid oxidation, if maintained for a long period of time, is believed to impair MT oxidative phosphorylation, causing damage to the electron-transport chain and depressing MT Mg^{2+} ATPase [29–31]. In addition to the reduction of ATP reserves and depressed cardiac function [30, 31], MT dysfunction is associated with the formation of MT pores, leaking of MT proteins, and cellular dysfunction [9, 13, 24, 30, 85, 86]. Triglyceride synthesis is also remarkably upregulated in diabetic cardiomyopathy, leading to a phenomenon called lipotoxicity that is intimately related to cellular damage [9, 87]. Enhanced FFA uptake is associated with the accumulation of lipid droplets in the myocardium during the development of diabetic cardiomyopathy [9, 86].

Diabetes is intimately associated with defects in several metabolic pathways that are responsible for a marked increase in intracellular Ca^{2+} concentration [13, 18, 24, 73, 86, 88–95]. Ca^{2+}-handling defects in chronic diabetes are known to be related to SL and sarcoplasmic reticulum (SR) alterations that favor the occurrence of intracellular Ca^{2+} overload [96–99]. In this regard, MT are known to function as Ca^{2+} sinks, in the event of Ca^{2+} overload, in an attempt to maintain the normal cytoplasmic level of free Ca^{2+} [24, 73, 100, 101]. Although this mechanism is intended to be protective in nature, excessive MT Ca^{2+} uptake depresses MT phosphorylation activity [13]. Different drugs that are capable of attenuating Ca^{2+} overload, such as Ca^{2+} channel blockers and angiotensin-receptor antagonists, have been shown to ameliorate cardiac dysfunction in diabetic cardiomyopathy [40, 95, 102, 103].

It is becoming clear that oxidative stress contributes to the development of several diabetic complications [104–108], including diabetic cardiomyopathy [13, 85, 109–113]. Hormonal imbalance in diabetes, marked by elevated levels of angiotensin II, catecholamines, and endothelins, plays a significant role in promoting oxidative stress and cardiac dysfunction [13, 114]. Damaged MT [13, 115, 116] and advanced protein glycation, caused by hyperglycemia, are also known to result in the development of oxidative stress in chronic diabetes [117, 118]. Initially, cardiomyocytes cope with increased oxidative stress by boosting their natural antioxidant defenses. Elevated activities of superoxide dismutase, glutathione peroxidase, and other antioxidant enzymes have been reported in the diabetic rat heart [119–121]. Most likely, these initial compensatory mechanisms are eventually exhausted, resulting in oxidative stress and leading to subcellular remodeling and myocardial cell damage [13]. Some reports have indicated that antioxidants are effective in preventing diabetic cardiomyopathy and cardiac dysfunction [13, 122, 123] and thus provide evidence regarding the relevance of oxidative stress in the pathophysiology of diabetic cardiomyopathy (Fig. 2).

5 Conclusions

From the foregoing discussion, it is apparent that a defect occurs in the process of energy production that leads to depression of ATP stores in the diabetic heart, primarily because of a shift in the balance between the utilization of glucose and the utilization of FFA as substrates by the myocardium. Excessive utilization of FFA for a prolonged period is considered to impair MT function with respect to oxidative phosphorylation and the electron-transport system. MT defects also includes opening of MT pores for leakage of cytoplasmic proteins that lead to the development of myocardial cell damage in the form of diabetic cardiomyopathy. Abnormalities in myocardial metabolism also promotes the occurrence of oxidative stress and intracellular Ca^{2+} overload, which results in the activation of different proteases and defects in gene expression in the diabetic myocardium. During this process of subcellular remodeling caused by diabetes, MF become defective in respect to their ability to utilize ATP as well as sensitivity to Ca^{2+} for the generation of contractile force. Thus, not only is cardiac dysfunction the result of defects in energy production by MT, but also defects in energy utilization by MF play a critical role during the development of diabetic cardiomyopathy.

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