

## Regulation of ATP Flow by Calcium Sensitive Receptors in Diabetic Cardiomyopathy

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**Keywords:** Diabetic cardiomyopathy; Metabolic disorders; Pathogenesis

**Abstract:** Diabetes mellitus (DM) is a common disease that seriously endangers people's health. Diabetic patients are prone to complicated cardiomyopathy or heart failure, which has become an important cause of death for diabetic patients. Diabetic cardiomyopathy (DCM) is a specific cardiomyopathy, which is mainly caused by cardiac microvascular disease and myocardial metabolic disorder due to hyperglycemia. It is characterized by left ventricular hypertrophy and diastolic dysfunction with or without systolic dysfunction. The specific pathological changes of diabetic cardiomyopathy is one of the common hidden cardiovascular complications of diabetes. Its clinical manifestations include heart failure, angina pectoris and arrhythmia, and it can exclude cardiomyopathy caused by hypertension, coronary heart disease, heart valve disease and other heart diseases. It is of great significance to study the pathogenesis of diabetic cardiomyopathy for the prevention and treatment of diabetes and its cardiovascular complications. Based on this, this paper analyzes the role of calcium sensitive receptors in the regulation of ATP flow in the pathogenesis of diabetic cardiomyopathy.

### 1. Introduction

Diabetes mellitus (DM) is an endocrine metabolic disease caused by a series of substance metabolism disorders such as sugar, protein, fat and the like caused by absolute or relative insufficiency of insulin secretion and reduction of insulin sensitivity of target tissue cells. Its chronic complications are extremely extensive and can affect almost all tissues and organs of the whole body [1]. Nowadays, the incidence of diabetes is increasing rapidly in the world, and diabetes has become one of the major endocrine diseases with the highest mortality rate in the world. The pathogenesis of diabetic cardiomyopathy is not completely clear. Researchers have explored its pathogenesis from different fields such as gene regulation and cell biology. Excluding atherosclerosis, hypertension and other potential causes, an independent primary disease of myocardial structural and functional abnormalities caused by diabetes, called diabetic cardiomyopathy, can cause death of patients [2]. The thickening of the capillary basement membrane causes extensive and long-lasting chronic ischemia and hypoxia in the myocardium, causing myocardial degeneration and small focal necrosis, and finally leading to cardiac insufficiency. Epidemiological studies have found that more than 70% of diabetic patients die from diabetic cardiomyopathy, and the mortality rate is 2-4 times that of non-diabetic people [3]. Cardiovascular disease occurs earlier and more severely in the diabetic patients than in the general population, and is the leading cause of death in diabetic patients.

The damage of diabetes to the cardiovascular system mainly involves the large, medium and small blood vessels and microvasculature of the heart, mainly including non-specific coronary atherosclerotic heart disease, specific cardiomyopathy and arrhythmia caused by diabetic heart disease and autonomic neuropathy Or cardiac insufficiency [4]. The specific disease of diabetic cardiomyopathy is one of the common cardiovascular complications of occult diabetes. Its clinical manifestations include heart failure, angina pectoris, arrhythmia, and can rule out hypertension, coronary heart disease, heart valve disease, and other cardiomyopathy caused by heart disease. Decreased mitochondrial biosynthesis may be the underlying cause of mitochondrial dysfunction in

diabetes. It can be seen that mitochondrial dysfunction induced by reduced mitochondrial biosynthesis plays an important role in the development of diabetic cardiomyopathy [5]. As an important organelle in eukaryotic cells, mitochondria can not only provide energy for cells to perform various life activities through oxidative phosphorylation, but also are closely related to the regulation of many important life activities in cells, such as maintaining ion stability State, generation of reactive oxygen species and apoptosis [6]. Diabetes due to long-term hyperglycemia leads to arteriosclerosis and microvascular disease, and early and severe damage to the heart, brain, kidney, eyes, nerves, skin and other organs occurs, and symptoms and signs of corresponding organs appear [7]. In-depth study of the pathogenesis of diabetic cardiomyopathy is of great significance for the clinical prevention and treatment of diabetes and its cardiovascular complications.

## **2. Pathogenesis of Diabetic Cardiomyopathy**

DCM is a widespread focal necrosis of myocardial tissue caused by diabetic cardiac microvascular disease and myocardial metabolic disorder. The early stage is generally characterized by diastolic dysfunction with reduced myocardial compliance and blocked diastolic filling, while the late stage is mainly characterized by systolic dysfunction and prone to congestive heart failure. Diabetic cardiomyopathy will eventually develop into heart failure without treatment, and currently there is no effective drug for heart failure. Therefore, early diagnosis and effective treatment of diabetic cardiomyopathy are particularly important. Mitochondrial biosynthesis inhibition is manifested by reduction of mitochondrial number and ATP production. However, the cause of mitochondrial biosynthesis inhibition is not completely clear. UCP2 is a carrier protein that widely exists on mitochondrial inner membrane of various human tissue cells. It has proton channel function and can reduce proton concentration gradient on both sides of mitochondrial inner membrane, make substrate oxidation and ADP phosphate uncouple, and reduce ATP generation. The abnormal lipid metabolism is mainly due to the increased fatty acid oxidation function of cardiac muscle cells, and the intermediate products in the utilization process also cause damage to the cardiac muscle. When diabetic cardiomyopathy occurs, the heart's systolic and diastolic functions are impaired, which is manifested in a decrease in the maximum rate of left ventricular pressure, a decrease in the maximum rate of left ventricular pressure, and an increase in the time required to reach the maximum rate of left ventricular pressure [8]. Diabetic cardiomyopathy is an independent primary disease that does not depend on coronary artery disease, hypertension, and other known heart diseases. However, the pathogenesis of diabetic cardiomyopathy has not been fully understood, and the establishment of animal models is relatively delayed.

Electrophysiological changes of DCM myocardial cells are the pathophysiological basis of changes in cardiac contractile function and ventricular arrhythmias. The related researches on DCM electrophysiological changes at home and abroad in recent years are reviewed. Because mitochondrial DNA is mainly synthesized on the inner membrane of mitochondria, and oxidative phosphorylation sites are also on the inner membrane of mitochondria, plus mtDNA lacks the protection of histones or DNA-binding proteins, mtDNA is extremely vulnerable to oxidative damage, leading to mitochondrial biosynthesis obstacle. In addition to oxidative stress, which can damage mitochondrial DNA, it can also damage mitochondrial respiratory enzymes, reduce their activity and reduce ATP production. Oxidative stress refers to the imbalance between oxidative damage and antioxidant defense caused by excessive production of reactive oxygen species or weakening of the body's antioxidant capacity. Cardiovascular disease is the most important factor to increase the morbidity and mortality of diabetic patients. The characteristics of DCM cause left ventricular dysfunction, but it is independent of coronary heart disease, atherosclerosis and other factors, which is the most important factor for diabetes patients to eventually cause heart failure. Diastolic dysfunction is described as the change of central muscle function in early stage of diabetic cardiomyopathy, and systolic dysfunction mainly occurs in late stage of the disease.

### 3. Calcium Sensitive Receptors Regulate ATP Flow

Glucose is a component of body energy metabolism. When glucose metabolism in cells is abnormal, it will lead to dysfunction of various organs in the body. When cardiomyopathy occurs, the ability of myocardial cells to utilize glucose decreases, ATP content decreases, and abnormal glycosylation occurs in sarcoplasmic reticulum calcium pump. Hyperglycemia is an important factor in the occurrence and development of DCM, which can cause degeneration, hypertrophy and necrosis of normal myocardial cells. Adenosine diphosphate polymerase intercepts GAPDH and induces ribose to modify protein, making glucose undergo glycogenolysis cascade reaction and participating in cell damage induced by high glucose. In the state of chronic insulin deficiency and resistance, glucose utilization is impaired, and the energy source of myocardial cells is almost all fatty acid beta-oxidation. AMPK may activate GLUT4 by regulating PI3K signaling pathways related to cell survival, metabolism and glucose metabolism, thus promoting glucose transport. Insulin resistance activates various lipases, promotes the hydrolysis of triglycerides in adipocytes into FFA and glycerol and releases them into blood, thus increasing the FFA level in plasma. Adiponectin is a kind of vasoactive peptide derived from adipocytes. Its concentration in plasma is high, which has anti-inflammatory and protective effects on myocardial endothelial cells. It is closely related to insulin resistance and hyperlipidemia. The mechanism of myocardial dysfunction caused by hyperlipidemia is not clear, but the underlying mechanism has been confirmed. For example, long-chain fatty acids can change the phospholipid composition and mitochondrial membrane structure in plasma, and then change the structure of myocardial cells.

100 patients with diabetic cardiomyopathy were selected and included in the criteria: 1. All patients met the WHO diagnostic criteria and related classification criteria for diabetes; 2. All patients were informed and agreed; 3. Fasting blood glucose ( $14.5 \pm 2.8$ ) mmol / L; 4. Life could be self-care without serious complications; 5. No mental disorders, effective communication and exchange; 6. Conscious, able to cooperate independently or with the help of family members Nursing. Exclusion criteria: 1. Serious heart, liver and kidney failure; 2. History of mental illness and mental illness; 3. Serious illness, unable to cooperate with the study; 4. Patients with malignant tumors; 5. Unconsciousness, unable to cooperate with treatment and nursing. All patients were randomly divided into observation group and control group with 50 cases in each group. The age of the observation group was 55-77 years, with an average of ( $64.3 \pm 5.1$ ) years. The course of disease was 4-14 years, with an average of ( $6.7 \pm 3.4$ ) years. In the control group, the average age was ( $65.9 \pm 3.8$ ) years, the course of disease was 2-15 years, the average was ( $7.2 \pm 3.7$ ) years. There was no significant difference between the two groups ( $P > 0.05$ ). The drug treatment of the two groups were basically the same. They were all treated with oral hypoglycemic drugs or insulin intensive therapy, antihypertensive therapy, symptomatic therapy and other comprehensive treatment. Routine nursing was used in the control group. The observation group was given traditional Chinese medicine nursing on the basis of the control group, including diet and emotion. Through the evaluation of the patients' psychology, we can adopt the method of emotional winning for different emotional types.

After nursing, compared with the control group, the observation group had better satisfaction in the overall understanding of diabetes, the understanding of Chinese medicine diet therapy and the diet therapy effect, with statistically significant differences ( $P < 0.05$ ), as shown in table 1.

Table 1. Comparison of TCM medical conditions between the two groups of patients

Group	Lack of general understanding of diabetes	Lack of understanding of medical treatment	Not satisfied with food therapy	Can't persist for a long time
Control group	38 (76%)	42 (84%)	24 (48%)	40(80%)
Observation group	20(40%)	16 (32%)	14(28%)	22 (44%)

There was no significant difference between the two groups before nursing ( $P > 0.05$ ). After nursing, compared with the control group, FBG and p2hbg in the observation group were significantly reduced, with a statistically significant difference ( $P < 0.05$ ), as shown in Table 2.

Table 2. Comparison of blood glucose control levels between two groups of patients

Group	FBG/(mmol/L)		P2hBG/(mmol/L)	
	Before nursing	After nursing	Before nursing	After nursing
Control group	8.15±2.31	6.25±1.92	11.96±2.38	9.82±3.66
Observation group	7.88±2.29	5.37±1.84	12.22±2.48	8.03±2.27

Advanced glycation end products are brown polymers formed by a series of complex non-enzymatic reactions between carbonyl groups of glucose and amino groups of proteins. These glycosylation products have various structures and are not easy to be degraded by enzymes. This change is positively related to the decline of myosin function and is dose-dependent. Excessive lipid accumulation in myocardial cells can lead to lipid toxicity, interfere with many metabolic processes of cells, increase myocardial oxygen consumption, cause arrhythmia, decrease myocardial contractility and cardiac dysfunction, and the degree of myocardial cell damage is directly related to its intake of fatty acids. Hyperglycemia and insulin resistance are causal factors and play an important role in the pathogenesis of diabetic cardiomyopathy [9]. Insulin resistance can further worsen heart function by increasing endothelin secretion, activating RAAS and sympathetic excitation. Fatty acid oxidation needs more oxygen. The intermediates produced by fatty acid metabolic oxidation can damage the calcium balance of myocardium and aggravate myocardial dysfunction. Activation of AMPK can not only regulate glucose and lipid metabolism, but also inhibit the activation of extracellular signal regulated protein kinase induced by angiotension II to a certain extent, so as to improve cardiac hypertrophy caused by myocardial fibrosis and protect myocardial injury [10]. Traditional PKC subtype  $\beta 1$  is related to the level of vascular dysfunction in diabetes mellitus. Hyperglycemia and high free fatty acids can increase the production of diacylglycerol and activate oxidative stress under PKC. Excessive use of fatty acid oxidation in diabetic myocardium can inhibit the activity of pyruvate dehydrogenase, reduce the use of pyruvate, and affect the energy metabolism of myocardium.

#### 4. Conclusion

Diabetic cardiomyopathy refers to the heart disease that occurs in diabetic patients and cannot be explained by hypertensive heart disease, coronary atherosclerotic heart disease, heart valve disease and other heart diseases. The pathogenesis of diabetic cardiomyopathy may be related to the dysfunction of energy metabolism and abnormal calcium transport mechanism of cardiomyocytes. Too much lipid accumulation in cardiomyocytes will lead to lipotoxicity, interfere with many metabolic processes of cells, increase oxygen consumption of myocardium, cause arrhythmia, decrease of myocardial contractility and dysfunction of heart function, and the degree of injury of cardiomyocytes is directly related to the intake of fatty acids. The metabolic remodeling of cardiomyocytes in DCM is the pathophysiological basis of ventricular electrophysiological remodeling. Metabolic remodeling of DCM will lead to ATP deficiency, which leads to dysfunction of myocardial cells including ion pump dysfunction and metabolic disorder in myocardial cells, resulting in abnormal ion channel, exchanger, pump function and gene expression in myocardial cells. The onset of diabetic cardiomyopathy is hidden, and it is difficult to find it in the early stage. Irreversible lesions usually occur in myocardium when clinical diagnosis is made. Therefore, in the study of diabetic cardiomyopathy, it is very important to select an appropriate animal model that can highly simulate the clinical pathogenesis.

## Acknowledgements

1. The role of calcium sensitive receptors in regulating ATP flow in the pathogenesis of diabetic cardiomyopathy (SFGG-201902)
2. TSP1 / CD36 induces podocyte apoptosis in hypertensive nephropathy (SFGG-201410)

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