

Oxidative stress in cardiac and skeletal muscle dysfunction associated with diabetes mellitus

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(Received 8 November, 2010; Accepted 11 November, 2010)

Diabetes mellitus increases the risk of heart failure independently of underlying coronary artery disease. It also causes skeletal muscle dysfunction, which is responsible for reduced exercise capacity commonly seen in heart failure. The underlying pathogenesis is partially understood. Several factors may contribute to the development of cardiac and skeletal muscle dysfunction in heart failure and diabetes mellitus. Based on the findings in animal models, this review discusses the role of oxidative stress that may be involved in the development and progression of cardiac and skeletal dysfunction associated with diabetes.

Key Words: oxidative stress, diabetes mellitus, cardiac dysfunction, skeletal muscle dysfunction, heart failure

Diabetes mellitus often leads to heart failure (HF), even in the absence of any other risk factors such as coronary artery disease or hypertension, suggesting that diabetes itself causes a specific form of cardiomyopathic state.⁽¹⁾ Diabetes causes myocardial structural remodeling characterized by myocyte hypertrophy, interstitial fibrosis, and apoptosis,⁽²⁾ which increases cardiac muscle stiffness and may contribute to diastolic dysfunction. Diastolic dysfunction has been regarded as a hemodynamic hallmark seen in diabetes and ultimately contributes to the development of HF.^(3,4) Diabetes further worsens systolic dysfunction due to myocardial infarction (MI).^(5–7) Previous clinical studies have shown that patients with diabetes have a worse outcome after MI than patients without diabetes despite similar left ventricular (LV) ejection fractions and coronary patency rates.^(8,9)

The features of diabetic heart disease have been well identified, however, its pathogenesis and, in particular, the mechanisms underlying myocardial remodeling have not been fully elucidated. The excess production of reactive oxygen species (ROS), superoxide anion ($O_2^{\cdot-}$), H_2O_2 , and hydroxyl radical ($\cdot OH$), resulting in oxidative stress, is widely considered to be a cause of target organ damage such as the heart, kidney, and skeletal muscle, in diabetes.^(10,11) Therefore, oxidative stress may contribute to the development of cardiac and skeletal muscle dysfunction in diabetes.

Diabetic Heart

Diabetes mellitus causes both diastolic and systolic cardiac dysfunction,⁽¹²⁾ but an impairment of diastolic function usually occurs before systolic dysfunction develops. The impairment of diastolic function despite normal systolic function is thought to result from an increased myocardial stiffness.

A growing body of evidence suggests that the production of ROS is increased in the diabetic heart.⁽¹³⁾ Specifically, ROS are produced within the mitochondria of the diabetic heart.⁽¹⁴⁾ The first line of defense against ROS-mediated cardiac injury comprises several antioxidant enzymes including superoxide dismutase (SOD), catalase, and glutathione peroxidase (GSHPx). GSHPx is

a key antioxidant that catalyzes the reduction of H_2O_2 and hydroperoxides. It not only scavenges H_2O_2 but also prevents the formation of other more toxic radicals such as $\cdot OH$. GSHPx possesses a higher affinity for H_2O_2 than catalase. Furthermore, it is present in relatively high amounts within the heart, especially in the cytosolic and mitochondrial compartments.⁽¹⁵⁾ These lines of evidence imply the primary importance of GSHPx as a defense mechanism within the heart. Moreover, GSHPx is expected to exert greater protective effects against oxidative damage than SOD because greater dismutation of $O_2^{\cdot-}$ by SOD may result in an increase of H_2O_2 . Therefore, compared with SOD or catalase, GSHPx is thought to be more effective in protecting cells, tissues, and organs against oxidative damage.^(16,17) In fact, the mice with GSHPx gene overexpression were more resistant to myocardial oxidative stress as well as remodeling and failure after MI.⁽¹⁸⁾ In the diabetic heart, the reduction of myocardial oxidative stress by GSHPx overexpression was associated with the attenuation of diastolic dysfunction, myocyte hypertrophy, and interstitial fibrosis.⁽¹⁹⁾ These findings are consistent with previous studies demonstrating that ROS are involved in the structural alterations of the extracellular matrix collagens.^(20,21) The decline in myocardial fibrosis by GSHPx overexpression may contribute to the physiological improvement of diastolic properties.

There may be several factors whereby oxidative stress contributes to myocardial remodeling in diabetes. First, oxidative stress is involved in cardiac myocyte hypertrophy and apoptosis. A subtle increase in ROS caused by partial inhibition of SOD results in hypertrophy and apoptosis in isolated cardiac myocytes,⁽²²⁾ both of which are thought to contribute to diabetic myocardial damage. Specifically, the incidence of apoptosis is increased in the diabetic heart,⁽²³⁾ which may cause loss of myocytes, compensatory hypertrophy of residual myocytes, and interstitial infibrosis.⁽²⁴⁾ Myocyte necrosis may also be involved in the increased fibrosis from the diabetic heart. Second, oxidative stress induces the activation of matrix metalloproteinases (MMPs). We have demonstrated that MMP-2 activation plays an important role in the pathophysiology of cardiac remodeling.⁽²⁵⁾ Moreover, MMPs have been shown to be activated by ROS in cardiac fibroblasts.⁽²⁶⁾ On the basis of these findings, increased ROS may contribute to the activation of MMP and thus to the development of interstitial fibrosis in diabetes. Third, a possible role for growth factors in diabetes-related end-organ complications is increasingly being recognized. Transforming growth factor (TGF)- β and connective tissue growth factor (CTGF) can induce the production of collagen and fibronectin from cardiac fibroblasts and myocytes, and increased expression of both factors contributes to the development and progression of cardiac remodeling in diabetes.^(27,28)

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Post-MI Diabetic Heart

Previous clinical findings demonstrated that patients with diabetes have a worse outcome after MI than that of patients without diabetes despite similar coronary patency rate and baseline LV ejection fraction.^(8,9) Furthermore, in the clinical study of patients with HF, diabetes reduced long-term survival independent of the etiology of HF and baseline LV ejection fraction.⁽²⁹⁾ The poor outcomes in patients with diabetes have been shown to be related with the progression of HF.⁽⁵⁻⁷⁾

Streptozotocin induces diabetes in rodents by chemical destruction of insulin-producing β -cells of the pancreatic islets, which thus models type 1 diabetes resulted from an auto immune-mediated loss of β -cell mass.⁽³⁰⁾ Hyperglycemia induced by streptozotocin exaggerates LV remodeling and failure after MI.^(31,32) In contrast, type 2 diabetes is typically preceded by obesity and associated metabolic abnormalities such as insulin resistance and dyslipidemia. Type 2 diabetes can be modeled by feeding a high-fat diet (HFD) in mice.⁽³³⁾ A HFD leads to insulin resistance, impaired glucose tolerance, an increase in body fat and dyslipidemia, and eventually fasting hyperglycemia. We demonstrated that HFD induced type 2 diabetes characterized by insulin resistance and obesity in mice and exacerbated LV remodeling and failure after MI.⁽³⁴⁾ Similarly, in Goto Kakizaki rats, a nonobese type 2 diabetes model, the progression of HF was accelerated after MI.⁽³⁵⁾ Therefore, either type 1 or type 2 diabetes exaggerates post-MI LV remodeling and failure.

The production of ROS is increased in post-MI hearts, and pharmacological and genetic interventions to scavenge ROS can ameliorate this disease process.^(36,37) Importantly, the activation of NAD(P)H oxidase enhances oxidative stress and plays an important role also in the progression of post-MI diabetic heart⁽³⁴⁾ as in other diabetic complications.⁽³⁸⁻⁴⁰⁾

Skeletal Muscle Dysfunction in Diabetes Mellitus

In patients with type 2 diabetes, the exercise capacity is limited⁽⁴¹⁾ and the lower exercise capacity is a significant independent predictor for mortality.⁽⁴²⁾ Exercise intolerance is generally believed to be due to the abnormalities in the energy metabolism in skeletal muscle.⁽⁴³⁾ Moreover, mitochondrial fatty acid β -oxidation and mitochondrial respiration were impaired in skeletal muscle from patients with type 2 diabetes.⁽⁴⁴⁾ These results suggest that diabetes may adversely affect mitochondrial function in skeletal muscle and lead to exercise intolerance. However, the pathogenesis of skeletal muscle dysfunction in type 2 diabetes remains undefined. Systemic oxidative stress has been reported to be increased in type 2 diabetes.⁽⁴⁵⁾ Moreover, the mitochondrial structure and function were impaired in skeletal muscle from HFD-fed rodents with the altered oxidative stress markers.⁽⁴⁶⁻⁴⁸⁾ Therefore, increased oxidative stress in skeletal muscle may impair mitochondrial function and limit the exercise capacity in type 2 diabetes.

We demonstrated that the exercise capacity was limited in the diabetic mice induced by HFD feeding.⁽⁴⁹⁾ This limitation of maximal exercise capacity was accompanied by a decrease of peak $\dot{V}O_2$. Coincident with these alterations, mitochondrial respiratory activity, electron transport chain (ETC) complex I and III activities and skeletal muscle mitochondrial content were decreased in the HFD mice. These findings are supported by the previous studies in patients with insulin resistance or type 2 diabetes, in which mitochondrial ATP production and state 3 respiration were decreased in skeletal muscle.⁽⁴⁴⁾ Moreover, mitochondrial oxidative phosphorylation genes including ubiquinol

cytochrome *c* reductase binding protein, a subunit of complex III, were downregulated in skeletal muscle from patients with diabetes, and their expression levels were positively correlated with peak $\dot{V}O_2$.⁽⁵⁰⁾ Accordingly, the metabolic abnormalities in the mitochondria from skeletal muscle can well explain a decrease in the exercise capacity and peak $\dot{V}O_2$ in the diabetic mice.

Importantly, chronic administration of apocynin in the HFD mice significantly ameliorated the limited exercise capacity as well as mitochondrial dysfunction in skeletal muscle without affecting glucose metabolism or body fat. Therefore, increased oxidative stress causes mitochondrial dysfunction in skeletal muscle and contribute to exercise intolerance in diabetes. These findings are in agreement with our previous study that the exercise capacity was reduced in conditions in which $O_2^{\cdot-}$ was increased in heterozygous manganese SOD gene knockout mice.⁽⁵¹⁾ The exercise capacity has been reported to be decreased also in rats fed vitamin E-deficient diets.⁽⁵²⁾ Therefore, oxidative stress and mitochondrial dysfunction in skeletal muscle play a crucial role not only in the development of insulin resistance but also exercise intolerance in type 2 diabetes.

The decrease of mitochondrial ETC complex I and III activities can potentially be explained by direct oxidative damage to mitochondrial complexes.⁽⁵³⁾ Mitochondria can be the primary target for oxidative damage when ROS production exceeds the capacity of the endogenous ROS scavenging system. $O_2^{\cdot-}$ can easily impair these ETC complexes because they include iron-sulfur center.⁽⁵⁴⁾ In addition, oxidative damage to mitochondrial DNA can also result in the decrease in ETC complex activities.⁽⁵⁵⁾ Furthermore, the impaired mitochondrial DNA may adversely affect mitochondrial biogenesis.

An explosive increase of patients with type 2 diabetes is a growing medical as well as public health problem in industrialized countries. Therefore, the development of novel therapeutic approaches for diabetes is an important goal for further investigation. The first line in the prevention and treatment of diabetes is the lifestyle modification including diet and physical exercise. Exercise training can increase mitochondrial oxidative capacity in skeletal muscle and delay or prevent diabetes by increasing insulin sensitivity. However, the limited exercise capacity might prevent the completion of proper exercise in patients with type 2 diabetes. Therefore, therapies designed to regulate oxidative stress and maintain mitochondrial function in skeletal muscle are expected to increase the exercise capacity, which may be beneficial in the treatment of diabetes and the prevention of cardiovascular diseases.

Conclusion

To improve the outcomes of patients with HF, the development of therapeutic strategies based on a novel insight into the pathophysiology of cardiac and skeletal muscle remodeling is critically needed.⁽⁵⁶⁻⁵⁸⁾ Therapies designed to interfere with oxidative stress could be beneficial to prevent not only diabetic heart disease but also skeletal muscle dysfunction in diabetes.

Conflict of Interest

No Potential conflicts of interest were disclosed.

Acknowledgments

The work presented in this article was supported in part by grants from the Ministry of Education, Science and Culture, Japan (No. 17390223, 17659223, 20117004, 21390236).

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