Benefit and risk of exercise on myocardial function in diabetes
Shiyan Li, Bruce Culver, Jun Ren

Division of Pharmaceutical Sciences and Graduate Neuroscience Program, University of Wyoming College of Health Sciences, University of Wyoming, College of Health Sciences, PO. Box 3375, Laramie, WY 82071-3375, USA

Accepted 11 March 2003

Abstract

Regular physical activity promotes cardiorespiratory fitness and has been considered a cornerstone for non-pharmacological treatment of more than 17 million Americans with diabetes mellitus. Physical exercise has been shown to positively affect certain cardiovascular risk factors such as insulin resistance, glucose metabolism, blood pressure and body fat composition, which are closely associated with diabetes and heart disease. With the increasingly sedentary lifestyle in our society, routine daily exercise of moderate intensity is highly recommended to reduce cardiovascular risk, the leading cause of death in diabetic patients. Exercise produces many beneficial effects to the heart function such as reduced incidence of coronary heart disease, attenuated severity of diabetic cardiomyopathy, improved cardiac performance, cardiac reserve and autonomic regulation. Nevertheless, many diabetic patients do not appear to gain much benefit from exercise or may even be at risk of performing physical exercise. This review summarizes the benefit and risk of exercise on diabetic heart function, with a special emphasis on myocardial and autonomic function.

© 2003 Elsevier Science Ltd. All rights reserved.

Keywords: Diabetes mellitus; Myocardial contractility; Exercise; Benefit; Risk

1. Introduction

Diabetes is caused by failure to maintain blood glucose at a stable level in the face of the normal fluctuations of supply and demand. Type 1 or insulin-dependent diabetes mellitus, in which the insulin secretagogues in the pancreas are damaged early in life, and the more insidious type 2 or non-insulin-dependent diabetes mellitus, where environmental and dietary overload destroy the blood glucose regulatory function, may both lead to severe complications such as cardiomyopathy, neuropathy, retinopathy and nephropathy [1]. It is predicted that the incidence of diabetes may be doubled over the next two decades largely due to the sedentary lifestyles and an ever growing cluster of pre-diabetic syndromes including syndrome X, obesity, and insulin resistance [2–4]. All of these metabolic disturbances are considered major risk factors for development of heart dysfunction and congestive heart failure. Diabetic cardiomyopathy is a distinct disease entity independent of macro- and micro-vascular diseases frequently seen in diabetic patients. It is characterized by ventricular dysfunction and abnormal intracellular Ca²⁺ homeostasis and contributes directly to the myogenic cardiac dysfunctions in diabetic individuals [5–8]. The increased risk of heart diseases, especially diabetic cardiomyopathy, in diabetes warrants stringent treatment of hyperglycemia and dyslipidemia. The most commonly used therapeutic regimes in diabetic patients with heart dysfunctions, such as low ejection fraction, presently encompass angiotensin-converting enzyme inhibitors, digoxin, diuretics, β-blockers, and spironolactone. Conversely, control of heart rate with β-blockers or Ca²⁺ antagonists is essential if impaired diastolic function is predominant. In addition, the insulin-sensitizing agents are recommended in treatment of diabetes over the insulin-secretion-enhancing agents to avoid hyperinsulinemia and insulin resistance. In addition to pharmacological interventions, primary care for patients with diabetes also includes lifestyle modifications such as smoking cessation, weight control, exercise and dietary restriction [9–11]. Research has shown that routine exercise regimes reduce blood glucose, blood pressure, body weight and body fat, and improves lipid profiles [12–15]. However, the direct relationship of exercise program and heart function in diabetes has rarely been elucidated. This review will attempt to correlate the benefit and risk of exercise on myocardial dysfunctions in diabetes. We hope to provide some insight into understanding the complex etiology of diabetic cardiomyopathy.
and the suitability of applying exercise to improve cardiac dysfunction in patients with diabetes.

2. Myocardial contractile dysfunction in diabetes

Diabetes has been shown to independently predispose the heart to multiple abnormalities independent of atherosclerosis, hypertension, coronary artery disease and valvular disease [5,6,16,17]. Evidence from both human and experimental animals has demonstrated the existence of a specific diabetic cardiomyopathy independent of macrovascular coronary artery complications [5,7]. Diabetic cardiomyopathy is believed to contribute to the high incidence of cardiac dysfunction and mortality in both types of diabetes [5,8]. Diastolic dysfunction is the most prominent mechanical defect in diabetic cardiomyopathy and is characterized by decreased compliance and slower rates of myocardial relaxation [5-7]. Both systolic and diastolic dysfunctions have been characterized as prolonged contraction and relaxation, reduced velocity of contraction and relaxation, and depressed myocardial contractility in whole heart, tissue, and isolated ventricular myocytes from both diabetic patients and experimental animals [5-7,16]. Although the pathogenesis of diabetic cardiomyopathy is not completely understood, several speculations have been made regarding the mechanism of action for diabetic cardiomyopathy, including reduced energy production due to decreases in mitochondrial respiration and pyruvate dehydrogenase activity, dysfunctional cardiac contractile and regulatory proteins such as myosin isoform, myosin Ca\(^{2+}\) ATPase, as well as impaired intracellular Ca\(^{2+}\) homeostasis [17-20]. A shift in myosin isoforms has been reported in diabetes from the fast type (V\(_1\)) to the slow type (V\(_3\)), which may contribute to the depressed velocity and prolonged duration of contraction [21,22]. Under normal conditions, the V\(_3\) isoform (two α heavy chains) is predominant in cardiac muscles, allowing the heart to contract with a high velocity, and the highest ATPase activity. The V\(_3\) isoform consists of two β\(_2\) chains with slow contraction velocity and low ATPase activity. Besides the myosin filament, the troponin–tropomyosin complex (TnTm) may be involved in diabetic mechanical dysfunctions. Tropomyosin normally resides in the grooves of the actin thin filaments and is anchored to troponin. The troponin I subunit (TnI) is bound to the actin–tropomyosin complex covering the binding sites of actin for myosin heads, thus inhibiting interaction between actin and myosin. A modification of the TnI subunit has been demonstrated in diabetes and leads to reduced activity of cardiac actomyosin Ca\(^{2+}\)- Mg\(^{2+}\)-ATPase. Since phosphorylation of TnI is immediately associated with extracellular Ca\(^{2+}\)-contractile force relationship, alteration in TnI may directly contribute to depressed myocardial contractility in diabetes [23].

It has been suggested that diabetic mechanical dysfunctions may be underscored by the abnormal intracellular Ca\(^{2+}\) handling. We have shown prolonged intracellular Ca\(^{2+}\) transients associated with cardiac excitation–contraction (E–C) coupling on a beat-to-beat basis, and this may be responsible for the impaired relaxation [6,16,17]. The reduced cytosolic Ca\(^{2+}\) clearing may be a result of impaired sarcoplasmic reticulum Ca\(^{2+}\)-ATPase (SERCA) and/or other Ca\(^{2+}\) regulating proteins such as Na/Ca exchanger [17,20,24]. During relaxation, SERCA and Na/Ca exchanger function to extrude cytosolic Ca\(^{2+}\), allowing the myocardium to relax during diastolic phase [25]. Decreased activity in SERCA and/or Na/Ca exchanger would lead to a chronic rise in [Ca\(^{2+}\)], and eventually a state of Ca\(^{2+}\) overload. Insulin deficiency was reported to significantly reduce the activity of Na/Ca exchanger in diabetic hearts [24]. Not surprisingly, impaired SERCA and Na/Ca exchanger protein abundance or function may be partially restored with normalization of glucose and insulin levels, or supplementation of insulin analogue insulin-like growth factor I (IGF-1) [20]. Although these findings are not sufficient to explain why cardiovascular abnormalities still persist in diabetic patients even with insulin therapy, it suggested that untreated diabetes (increased blood glucose and decreased insulin) would inevitably impair the function of key cardiac Ca\(^{2+}\) regulatory proteins such as SERCA and Na/Ca exchanger leading to slowed intracellular Ca\(^{2+}\) clearing and intracellular Ca\(^{2+}\) overload in diabetic hearts. In addition, diabetes has been shown to depress the myofilament Ca\(^{2+}\) sensitivity [16,26], which also contributes to the reduced cardiac contractility in diabetes.

3. Benefit of exercise on myocardial function in diabetes

The most significant physiological adaptation of the heart during exercise is manifested as increased delivery of blood to peripheral vasculature to meet the enhanced demands of the musculoskeletal and pulmonary systems [27-29]. This is usually achieved with an increased cardiac output (CO) through a combined increase of heart rate (HR), stroke volume (SV), and/or myocardial contractility [30,31]. Physical exercise is often associated with an increased myocardial chronotropic and inotropic response to the sympathetic system (β-adrenergic response) as well as improved intrinsic myogenic tone [27]. Although the parasympathetic system is known to participate in the tonic control of myocardium, it is predominantly at rest. In this section, we will focus on sympathetic and myogenic regulation of myocardial function in diabetes during exercise.

Physical exercise is well known to improve glucose and lipid metabolism and reduce insulin resistance [32]. Research has shown that physical exercise of sufficient intensity and duration improves cardiac performance and cardiac reserve in healthy non-diabetic individuals [27]. The impact of exercise on cardiac function in diabetes displays somewhat similar patterns although patients with mild hyperglycemia show a better response than those patients with severe
is decreased left ventricular ejection fraction (LVEF) [38]. A significant lowering of cardiac contractile dysfunction and cardiac mortality was seen in insulin resistant and type 2 diabetic patients with regular physical exercise of moderate intensity [34]. Although the mechanism of action involved in the beneficial action of exercise in diabetic cardiac dysfunction is not fully clear, major attention has focused on the effect of exercise on the autonomic function and cardiac contractile regulation of myogenic origin. It was suggested that exercise increases the CO of both sedentary and diabetic animals at high, but not low, preload, thus attenuating the depressed cardiac performance in diabetes and severity of diabetic cardiomyopathy [35]. It was also reported that exercise improves cardiac pumping function, lowers plasma triglyceride levels and increases carnitine content in diabetic hearts [36,37]. A close comparison of diabetic-associated cardiac function at rest and during exercise has provided some useful information regarding the etiology of diabetic cardiomyopathy. As mentioned, diabetes induces prolonged contraction and relaxation duration at rest, associated with a significantly decreased CO during “occasional” exercise. The most prominent cardiac dysfunction under “occasional” exercise in diabetic patients is decreased left ventricular ejection fraction (LVEF) [38]. The decreased (or unchanged in some reports) LVEF during exercise cannot provide the cardiopulmonary system with a sufficient supply of blood and oxygen to maintain homeostatic conditions. In addition to decreased LVEF, left ventricular diastolic dysfunctions have also been observed in diabetic hearts [36,37]. A close comparison of diabetic-associated cardiac function at rest and during exercise has been provided for the diabetic pumping function, lowering plasma triglyceride levels and increases in carnitine content in diabetic hearts during resting condition. However, early apexcardiographic relaxation time (EARTc) does not differ significantly between normal and diabetic subjects during resting condition. It is possible that exercise may improve cardiac function at rest and during exercise may be attributed to an array of myocardial alterations such as a myosin isozyme switch (V1 → V2) and increased phosphorylation of cardiac inhibitory protein TnI [22,23]. The inability to remove intracellular Ca2+ from the cytosolic space as a result of depressed SERCA and Na/Ca exchanger function in diabetes is also evident during exercise manifested as prolonged early apexcardiographic relaxation time (EARTc) in diabetic hearts. Little effect has been reported regarding any direct improvement of the messenger RNA, protein abundance and function of these cardiac contractile proteins. It is possible that exercise may improve cardiac function through indirect actions on plasma lipid profiles and insulin sensitivity. Both of these actions would improve cardiac glucose utilization. This notion was supported by our preliminary finding that exercise training and dietary supplementation of fish oil or bezafibrate may effectively reverse insulin resistance-induced cardiac contractile dysfunctions in ventricular myocytes [41]. Exercise has been shown to attenuate the reduction in myocardial GLUT-4 transporters [42] and up-regulate sarcolemmal GLUT-4 protein in diabetic rats [43]. Exercise-associated improvement of insulin sensitivity may play an essential role in this process since the GLUT-4 depression and hemodynamic changes may be reversed with insulin treatment. Insulin also enhances LVEF during exercise in diabetics possibly due to improved ventricular contractility under both exercise and insulin treatment [44]. In addition to the above mentioned possible myogenic origins of beneficial actions of exercise on diabetic cardiac dysfunction, improvement of left ventricular geometric characteristics due to exercise may have also contributed to the action of exercise on diabetic hearts. Exercise has been shown to normalize the myocardial collagen levels in diabetes [45].

One important aspect of exercise on cardiac function in normal individuals has been associated with its ability to enhance autonomic function. It is speculated that the autonomic response may play a beneficial role of exercise in diabetic cardiac dysfunction. Release of norepinephrine, which is synthesized and stored in cardiac sympathetic fibers, is considerably increased during exercise and leads to improved cardiac performance in normal individuals. Activation of the β1 receptor by norepinephrine activates the stimulatory G protein—Gαs and adenylyl cyclase. The resultant accumulation of cAMP leads to a rise of intracellular Ca2+ and enhanced cardiac contractility. Diabetic cardiomyopathy has been shown to display reduced adrenergic sensitivity, with specific molecular alterations in the β-adrenergic receptor—G protein-adenylate cyclase signal transduction system. The depressed catecholamine responsiveness and impaired sympathetic nervous function may directly prompt the onset of diabetic left ventricular dysfunction or diabetic cardiomyopathy [46,47]. The diabetes-associated sympathetic defect was further confirmed by the observation that the β-adrenergic agonist dobutamine fails to improve LVEF in diabetic patients with exercise-induced left ventricular dysfunction [48]. In addition, plasma norepinephrine levels are reported to be two to five-fold higher in diabetics than those of normal subjects [49]. It may be speculated that prolonged exposure of catecholamine may down-regulate the β-adrenergic receptors, decreased sensitivity of adenylylate cyclase and LVEF during exercise. These data suggest that the potential beneficial effects of the β-adrenergic receptor-adenylate cyclase system on membranes from ventricular tissue [50]. While a decrease in the number of β-adrenergic receptors would not allow the myocardium to respond properly to norepinephrine during exercise, a decrease in the activity of adenylylate cyclase may be due to modification of the β-adrenergic receptor-linked adenylylate cyclase system. Nevertheless, a recent report using streptozotocin-induced diabetic rats indicated that exercise improves diabetes-induced cardiac dysfunction and autonomic dysregulation [37]. Reduction in heart rates, seen in sedentary diabetic subjects, has been attributed to changes
in sinoatrial node. An increase in resting heart rate in trained diabetic rats was observed, confirming the important role of sinoatrial node changes in the heart rate in diabetes [37]. It may be speculated that the increase in resting heart rate in trained diabetic rats may be the result of improved intrinsic pacemaker regulation. It is suggested that exercise does not modify parasympathetic tone in diabetes, although a slight increase in vagal discharge was observed in trained rats [37]. Further investigation is still warranted to examine the impact of exercise on β-adrenergic receptor-linked adenylate cyclase system in diabetes.

4. Risk of exercise for myocardial function in diabetes

While exercise provides much benefit to diabetic patients, there are certain cardiovascular risks associated with increased severity of diabetes [39,51]. Benefit of exercise should be carefully weighed against the potential risk when advising patients [52]. In general, exercise may exaggerate hyperglycemia or hypoglycemia through increased hepatic glucose production or exercise-induced increased sensitivity [53–55]. The potential for hyperglycemia may be magnified in type 1 diabetes because of insufficient endogenous insulin. Exercise may precipitate angina pectoris, myocardial infarction, cardiac arrhythmias and sudden death if there is pre-existing coronary artery disease. Several long-term complications may be worsened by exercise. Diabetic autonomic neuropathy, for example, may lead to arrhythmia (prolonged QT intervals) in diabetic patients performing exercise [34]. In addition, diabetic patients with abnormal exercise echocardiography are at much higher risk of cardiac events such as cardiac death or nonfatal myocardial infarction than those patients with normal exercise echocardiography [56], suggesting that exercise itself may be a risk factor for certain diabetic populations. Another example is that diabetic patients with altered exercise plasma catecholamine response are associated with higher risk of cardiac-cerebrovascular events. The altered exercise plasma catecholamine response may be reflected as chronotropic incompetence and lower plasma epinephrine response to exercise due to abnormal sympathoadrenal function and autonomic neuropathy in diabetes [57]. Therefore, careful screening of long-term complications of diabetes is essential for diabetics before any exercise program is initiated [58,59]. For patients over 35 years of age, an exercise stress test should be conducted to screen for ischemic cardiac diseases that may not have been previously diagnosed [60–62]. It appears that inappropriate or heavy exercise may present more risk to older diabetic patients than younger ones. Functional myocardial disease or diabetic cardiomyopathy is less severe or even absent in children and young adolescents with diabetes, suggesting that manifestations of the myopathic state may not be expected during the pediatric years. Regular levels of habitual exercise are expected more likely to affect aerobic fitness rather than influences of the diabetic state itself in young diabetic patients [63].

5. Conclusion

Physical inactivity is an independent predictor of all cause mortality in diabetic patients [64]. Regular exercise of moderate intensity has been recommended as an important component of the treatment and management of diabetes. The benefit of exercise on diabetes lays not only on glucose control but also on body weight gain, one of the most powerful predictors for diabetes in genetically susceptible individuals. Obesity is increasing dramatically and half of the adults in developed countries are overweight. Considering little change in average caloric intake over the past two decades, it is not difficult to conclude that this increase in obesity is due to a reduction in physical activity. Thus, regular exercise of moderate intensity is the key to the prevention of weight gain and onset of type 2 diabetes. Since exercise may present both benefit and risk to the diabetic populations, only modest exercise, such as walking three times a week, is recommended to achieve a cardioprotective benefit [58]. The exercise program of the Diabetes Prevention Program aims at weekly expenditure of 2000 calories [65]. In addition to diabetes, epidemiologic evidence also suggests the benefit of physical activity in preventing cardiovascular events in non-diabetic individuals. To unveil the exact nature of the beneficial action of exercise on diabetic cardiac dysfunction, future studies should focus on the mechanism of action of modest exercise on ventricular contractile function such as the cardiac contractile protein and autonomic nervous component such as on β-adrenergic receptor-linked adenylate cyclase system. These studies will provide insight into the cellular pathophysiology of diabetes cardiac dysfunction and in particular may establish novel therapeutic avenues for the treatment and management of cardiac dysfunction in diabetes, and possibly obesity.

Acknowledgements

The work in Dr. Ren’s laboratory has been supported by American Diabetes Association and American Heart Association—Northland Affiliate.

References


