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Diabetic Cardiomyopathy and the Role of Regular Exercise in Preventing the Disease: A Review

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Abstract

Diabetes mellitus (DM) is a major global metabolic disorder currently affecting over 450 million people and this number is rising rapidly. Heart failure (HF) is the major cause of death among diabetic patients. The disorder is due to elevated blood glucose level beyond physiological range or hyperglycaemia (HG), which in turn leads to a number of long-term complications, including diabetic cardiomyopathy (DC) over time. Around 80% of all diabetics will eventually die from DC. If left untreated, DC has been shown to be a critical factor in HF, independent of atherosclerosis, hypertension and valvular malfunction. The inability to maintain glucose homeostasis in the myocardium compromises cardiac structure and function in human diabetic subjects and also in animals with experimental diabetes. Daily exercise is known to protect the heart from sudden cardiac death. Exercise training (ET) is a beneficial non-pharmacological intervention for the treatment of cardiovascular diseases (CVDs). ET can induce cardio-protection in normal hearts and also in a partially diseased heart through a range of molecular mechanisms. The cardio-protective effect of ET is associated with the improvement of antioxidant capacity, mitochondrial viability and it can activate physiological cardiac growth, which are all mediated via distinct cellular and molecular mechanisms compared to those in pathological hypertrophy. Beneficial cardiac protection following regular ET in diabetes has been reported in both clinical and experimental animal studies. ET is a cost-effective strategy for prevention and treatment DC. However, the cellular and molecular mechanisms underlying DC and HF in diabetes and how regular exercise can reverse the pathology are not fully clear and further research should be carried out.

Keywords: Diabetes mellitus, heart, cardiomyopathy, hyperglycaemia, exercise, function

Introduction

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Cardiovascular diseases (CVDs) are directly linked to DM and are responsible for about 80% of mortality in the diabetic population [1]. Diabetic cardiomyopathy (DC) is diabetes-mediated, resulting in pathological cardiac remodelling in the absence of coronary artery disease, hypertension and valvular disease. In fact, diabetes is a multi-factorial disease. Therefore, the mechanism underlying DC is complex. However, an understanding of that mechanism is essential for preventing heart failure (HF) caused by diabetes or reserving the pathological cardiac remodelling [2]. In fact, HF is one of the main causes of mortality in the world despite advances in drug and treatments [3]. Epidemiological data show that macro-vascular complications, including coronary artery disease (CAD), hypertension, heart failure, peripheral vascular disease (PVD) and stroke are more common 2-4 times among diabetic patients in comparison with non-diabetic people [4]. Renal failure and CVDs are the two major causes of morbidity and mortality in diabetic patients and hearts of diabetic patients are frequently in a compromised condition [5]. According to the Framingham study, the frequency of CAD is twice more common in diabetic patients of both genders [6]. DM increases the risk for heart failure by progressive weakening of cardiac function. It can also affect cardiac structure and function without causing changes in blood pressure and CAD [7]. This term was introduced in 1972 for the description of 4 patients with DM and HF, but without any signs of either hypertension or CAD [8]. DC represents the major cause of mortality and morbidity among diabetics [9]. It has been defined as ventricular dysfunction which occurs in diabetic patients independent of a recognized cause such as CAD or hypertension. The early stage of DC is a hidden subclinical period in which cellular structural changes lead initially to diastolic dysfunction, later to systolic dysfunction, and eventually to HF. The most common contributors to DC onset and progression are left ventricular hypertrophy, metabolic abnormalities, (mitochondrial dysfunction), extracellular matrix changes (fibrosis), small vessel disease (endothelial dysfunction), cardiac autonomic neuropathy, insulin resistance, oxidative stress, and apoptosis, all leading to cardiac remodelling [10]. DC is also accompanied by comorbidities such as obesity, hypertension and others. These complications often precede the development of systolic function, CAD and heart failure [11].

Historical Background of Diabetic Cardiomyopathy

DC affects the heart by enhancing fatty acid metabolism, suppressing glucose oxidation and modifying intracellular signalling, all of which lead to alteration in multiple steps of the excitation-contraction coupling (ECC) process, inefficient energy production, increased susceptibility to ischemia and contractile dysfunction [12]. The exact underlying mechanism of DC is still not fully clear, and several causes have been proposed including metabolic disorder, autonomic dysfunction, and interstitial fibrosis [13]. Metabolic disturbances such as altered lipid handling and substrate utilization, decreased mechanical efficiency, mitochondrial dysfunction, disturbances in non-oxidative glucose pathways and increased oxidative stress are all hallmarks of DC. Thus, the pathogenesis of DC is multifactorial and complex, eventually leading to an energetically compromised heart with reduced cardiac working capacity and heart failure [14]. This review highlights the available data about the development of DC, how ET may influence cellular, structural and functional changes in DC, and in particular, to further explore the effect of exercise training (ET) on mitochondrial biogenesis in DC and how ET preserves cardiac function and prevents myocardial apoptosis and fibrosis. Since this review is based on non-pharmacological intervention to treat DC, then much emphasis will be focused on ET as non-pharmacological intervention in the treatment of heart disease.

Historical Background of ET as Medicine

The history of ET as a treatment and prevention measure may be attributed to the ancient Greek Society. Exercise as medicine was first proposed by Greek philosophers during the 4th century B.C. Furthermore, Hippocrates wrote two books on regimen and noted that “eating alone will not keep a man well; he must also take exercise” [15]. The effect of ET in lowering glycosuria has been evident since 600 B.C,

when Shushruta, an Indian Physician, noted the reduction in the sweetness of urine from diabetic patients after ET [16]. Nowadays, it is well established that physical exercise continues to be one of the most valuable and cost- effective forms of non-pharmacological therapy. ET can induce cardio-protection in normal hearts through a range of molecular mechanisms [17]. ET was defined by the American College of Sports Medicine as "Any and all activity involving generation of force by the activated muscle(s) that results in disruption of a homeostatic state" [18]. ET is classified by the type, intensity, and duration of activity. Endurance exercise reflects prolonged and continuous periods of contractile activity (high repetition) against low resistance [19]. In contrast, resistance exercise (strength training) involves short periods of contractile activity (low repetition) against a high opposing resistance, while sprint exercise occurs during short periods of maximal (intense) repetitive contractile activity, where there is a short period of exercise against a low resistance, such as running a 100-m sprint race. However, sprint training can also be performed against high resistance, which results in a combination of resistance and endurance modalities, for example, running with added weights [18]. The beneficial cardiac impact of ET in diabetes management has been reported in clinical medicine [20, 21] and experimental animal studies [22, 23]. ET is a low-cost strategy for the prevention and treatment of DC. ET has a beneficial impact on diabetes-related systemic changes and it may also improve the metabolic disturbances of the diabetic myocardium. These changes are the result of both indirect effects, exercise-mediated systemic changes and direct effect originating from the high contractile activity of the heart during ET [14]. The cardio-protective effect of ET is associated with the improvement of antioxidant capacity and mitochondrial viability and activated physiological cardiac growth which are all mediated via distinct cellular and molecular mechanisms from those patients with pathological hypertrophy [24]. Similarly, in animal models, it has been shown that ET can prevent ventricular remodelling and attenuated derangement of glucose and lipid metabolism, and improve mitochondrial function and antioxidant capacity leading to ameliorated cardiac performance in early stage of DC [24].

Structural and Functional Changes in DC

DC leads to structural and functional changes in the heart. The structural changes are manifested by left ventricular hypertrophy, interstitial fibrosis, increased cell death or apoptosis and oxidative stress [25, 26]. DC also results in functional changes including a derangement in cellular calcium homeostasis, diastolic dysfunction, systolic dysfunction and impaired contractile reserve [27]. In type 2 diabetes (T2DM), left ventricular mass is an independent marker of cardiovascular risk. It often occurs independent of atrial blood pressure. Therefore, diabetes is an independent risk factor leading to left ventricular hypertrophy and myocardial stiffness [28]. DC is also characterized by interstitial fibrosis, mostly composed of collagen and perivascular fibrosis [29]. At the cellular level, prolongation of cardiac action potential duration (CAPD) has been consistently shown in diabetic hearts. Significant alterations in the ionic currents that constitute cardiac action potential (CAP) configuration have been proposed as the main culprit of this prolongation [30, 31]. The intracellular free Ca^{2+} concentration $[Ca^{2+}]_i$ is very essential for the myocardium contraction [32]. DC-induced abnormalities during cardiac contractility have been correlated with the intracellular Ca^{2+} changes. Diabetic cardiac dysfunction most likely arises due to changes in expression and/or activity of cellular mechanisms that regulate Ca^{2+} transport during cardiac cycle [33]. Thus, DC results in changes in biomechanical, contractile and hypertrophic properties changes of cardiac myocytes.

These changes could be a result of altered myocardial glucose and fatty acid metabolism due to DM. Chronic hyperglycaemia leads to non-enzymatic glycation of vascular and membrane proteins, producing advanced glycation end products (AGEs), reactive oxygen species (ROS) and reactive carbonyl species (RCS) [34]. AGEs may play an important role in the pathobiology of heart failure [35]. AGEs are either proteins or lipids that become glycated after exposure to sugars. They are prevalent in the diabetic vasculature contributing to the development of

atherosclerosis. Moreover, they have been shown to be increased in plasma by hyperglycaemia [35]. Accumulation of AGE in collagen was associated with reduced collagen turnover, indicating the possibility that cross-linking of collagen makes collagen resistant to hydrolytic turnover. Such AGE-mediated cross-linking of collagen is thought to be responsible for increased stiffness of arteries and the myocardium. In fact, AGEs are increased in the myocardium during T1DM and T2DM, and there are positive correlations of serum level of AGEs with ventricular isovolumetric relaxation time, arterial stiffness, and carotid intimal thickness all of which have been shown in diabetics [35]. There is a significant increase in the deposition of collagen around the vessel and between the myofibres of heart biopsies from diabetic patients. In addition, deposits of lipofuscin, which are brown pigment granules composed of lipid-containing residues, were found in left ventricular transmural biopsies. Myocardial triglyceride and cholesterol contents in these biopsies were measured and significant increases in these molecules were found in the heart tissue [2].

DC, Insulin, and Metabolic Alteration

Insulin has a vital role in the regulation of various aspects of cardiovascular metabolism and function. In fact, the human heart produces and uses between 3.5 and 5 kg of ATP every day to pump. The energy generation depends on the cardiac environment including coronary flow, blood substrate supply, hormones and nutritional status [36]. Alteration of myocardial substrate and energy metabolism are considered as significant factors for the development of DC [37]. DM is characterized by reduced glucose and lactate metabolism and increased fatty acid (FA) metabolism [38]. In the diabetic heart, the myocardial glucose transport is impaired because of decreased myocardial concentration of GLUT1 and GLUT4 protein and mRNA level [39]. A second mechanism of reduced glucose oxidation is via the inhibitory effect of fatty acid oxidation on pyruvate dehydrogenase complex due to high circulating FFA [40]. Insulin induces glucose uptake in cardiomyocytes by binding to insulin receptor (IR). IR undergoes auto-transphosphorylation which initiates a signalling cascade initiated by tyrosine phosphorylation of insulin receptor substrates (IRS), followed by phosphorylation of phosphatidyl-inositol-3 kinase (PI3K), phosphoinositide-dependent kinase 1 (PDK1), Akt, and protein kinase C (PKC). These events lead the glucose transporter type 1 (GLUT1) and type 4 (GLUT4) translocation to the membrane to facilitate glucose uptake into the cell. In the heart, contractile-mediated translocation of GLUT4 represents the major mechanism that regulates glucose entry in the beating heart, with GLUT1 playing a lesser role [41].

Insulin resistance and hyperinsulinemia are recognized as risk factors for DC [42]. In hyperinsulinemia and insulin resistance, a disturbance of insulin-mediated glucose metabolism occurs which can significantly worsen metabolic efficiency of both skeletal and cardiac muscle. Insulin affects the diabetic heart by both systemic metabolism abnormalities and direct effects on insulin signalling pathways that are intrinsic to the cardiac tissue [43]. In the evolution of insulin resistance, the initial change that develops in the hearts of animal models is the impairment in the ability of insulin to increase glucose transport [44]. A recent study revealed that insulin resistance is associated with cardiac contractile dysfunction. The authors of the study generate a new insulin resistant animal rat model on high cholesterol fructose (HCF) diet. HCF diet induced insulin resistance on both metabolic response tissue and the heart as well. These findings illustrate that insulin resistance is associated with metabolic alteration and consequently leading to the development of DC [43]. Circulating FAs and triglycerides (TGs) are increased by enhanced lipolysis in adipose tissue and lipoprotein synthesis in liver, resulting in hyperglycaemia and insulin resistance. When the FAs exceed the oxidative capacity of the heart, the FAs are converted to lipid-like TG or ceramide which can lead to lipo-toxicity and cell apoptosis [45]. Thus, DM leads to increased rates of FA oxidation and decreased rates of glucose oxidation.

DC and Fibrosis

Interstitial and perivascular fibrosis is a histological symptom of DC [8]. The extent of fibrosis correlates with heart weight. The pathogenesis of fibrosis in the diabetic heart is proposed to be due to diabetic micro-angiopathy. When the diabetic heart is

affected by hypertension or CAD, there may be additive micro-angiopathy and large vessel-induced ischaemia leading to diffuse myocardial scarring. The generalized fibrosis can result in increased wall stiffness and diastolic dysfunction [46]. Activation of the renin-angiotensin system (RAS) is known to have a role in the development of DC [40]. In the diabetic heart, Angiotensin II (Ang-II) receptor density and mRNA expression are elevated [47]. The activation of RAS in DM is associated with increased oxidative damage, fibrosis and cell apoptosis [48]. Inhibition of the RAS was shown to reduce reactive oxygen species (ROS) production in streptozotocin-induced type 1 diabetic rats, similar to the effect observed with antioxidant treatment [49]. Ang-II, given exogenously to rodents, has been shown to cause cellular changes within myocardium leading to hypertrophy and fibrosis [50].

Mitochondrial Dysfunction

Mitochondria play a significant role in energy production in cells. They are also involved in other phenomena such as ion homeostasis, free radical production, and ultimately cell death [51]. Mitochondria are the center of fatty acid and glucose metabolism. Diabetes can lead to impaired metabolism associated with mitochondrial dysfunction. Recent studies have shown ultrastructural and functional changes of diabetic cardiac mitochondria. DM affects the protein composition of diabetic mitochondria [52]. In a model of chronic type 1 diabetic mice, damage to mitochondria was indicated by impaired function and ultrastructure abnormalities. Damage was accompanied by indicators of mitochondrial biogenesis, including increases in 11 specific mitochondrial proteins, elevation of mRNA for the mitochondrial regulatory protein and increased total mitochondrial DNA area and number. These findings showed that mitochondria are a major focus of diabetes-induced damage to the heart [53]. Along with those findings, DM also leads to a decrease in mitochondrial efficiency for ATP production. A recent study demonstrated the relationship between impaired insulin signaling and altered mitochondrial energetics by using mice with a cardiac-specific deletion of the insulin receptor. In the study, the authors found that impaired myocardial insulin signaling promotes oxidative stress and mitochondrial uncoupling, which, were accompanied with reduced fatty acid oxidative capacity and impaired mitochondrial energetics [54]. Diabetic mitochondria also produce more ROS than normal mitochondria [55]. According to the molecular theory of DC, hyperglycemia (HG) is the main pathogenic factor [56]. HG stimulates the overproduction or pathophysiological levels of ROS and reactive carbonyl species (RCS). ROS and RCS are significant contributors to structural and functional abnormalities of the myocardium [56]. Mitochondria are the major source of ROS and RAC productions and depletion of antioxidants as depicted in the flow diagram of Figure 1.

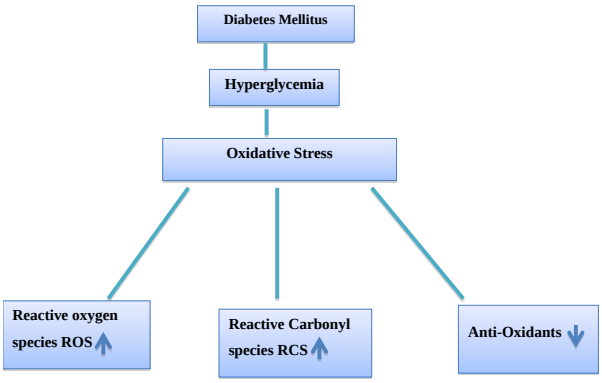

Figure 1. Flow diagram showing how DM can lead to hyperglycaemia and oxidative stress which in turn induced the production of ROS and RCS and a decrease in anti-oxidant capacity of the myocardium during diabetic cardiomyopathy.

Cellular sources of ROS generation within the heart include cardiac myocytes, endothelial cells and neutrophils. ROS induces cellular damage through many mechanisms including oxidation, interference with nitric oxide and modulation of detrimental intracellular signaling pathways. Thus, increased ROS leads to cardiac dysfunction by direct damage to proteins and DNA resulting in apoptosis [57]. RCS are diverse in chemical structures generated in different cell types including vascular smooth muscle cells of the body. They are derived from multiple sources, including auto-oxidation of glucose and lipids, triose pathway fluxes and from enzymes such as semicarbazide–sensitive amine oxidases and methylglyoxal synthase. In contrast, RCS also have

unique characteristic compared to ROS in that their half-lives are longer (minutes vs millisecond), and they are uncharged molecules, allowing them to migrate far distance from their site of production [58].

Impaired Ca^{2+} Homeostasis

Ca^{2+} is a major trigger, initiator, modulator, second messenger and regulator (signaling mechanism) of cardiac contractility. Most of the Ca^{2+} that activates contraction is released from sarcoplasmic reticulum (SR) through ryanodine receptors (RyRs). RyRs are themselves activated by the inducing Ca^{2+} through activation of voltage-dependent L- type Ca^{2+} channels and this mechanism is known as Ca^{2+}-induced Ca^{2+} release (CICR) [59]. The cytosolic Ca^{2+} ions in turn interact with contractile proteins. By binding to troponin C, the Ca^{2+} triggers the sliding of thin and thick filaments resulting in cardiac muscle contraction. Ca^{2+} then returns to diastolic levels mainly by activation of the SR Ca^{2+} pump (SERCA2a), the sarcolemma Na^{+}-Ca^{2+} exchanger (NCX), and the sarcolemma Ca^{2+} ATPase [7]. DM leads to mitochondrial dysfunction which contributes to the development of DC by altering ATP generation and Ca^{2+} movement as illustrated in Figure 2 [60]. Furthermore, it has been suggested that HG is associated with the alteration of the expression and function of RyRs and SERCA and this alteration may lead to impair myocardial systolic and diastolic function [27]. Thus, Ca^{2+} homeostasis is altered in DC by affecting the ability of SR to take up Ca^{2+} and the Na^{+}-Ca^{2+} exchanger, and the sarcolemma Ca^{2+} ATPase to pump Ca^{2+} out of the cell [61, 62], all leading to elevated diastolic Ca^{2+}. In streptozotocin (STZ)-induced type 1 diabetic rats, a depression in contraction and relaxation in myocytes was found in parallel with depression in the rise and decline of intracellular free Ca^{2+} concentration. The SR Ca^{2+} store and rates of Ca^{2+} release and reuptake into SR were depressed and the rate of Ca^{2+} efflux via sarcolemma Na^{+}-Ca^{2+} exchanger was also depressed. The depression in SR function was associated with decreased SR Ca^{2+}-ATPase and ryanodine receptor proteins and increased total and non-phosphorylated phospholamban proteins [63]. In DC, prolongation of cardiac action potential duration (CAPD) and slower decay of Ca^{2+} transient are consistently observed in DC. As for prolongation of CAPD, reduction in transient outward K^{+} (Ito) current has been shown in animal models of diabetes [64]. There is also a reduced expression of L-type Ca^{2+} channel activity which is also an additional abnormality in the heart [65]. The prolongation of APD is potentially a compensatory mechanism for preserving Ca^{2+} influx in cardiomyocytes with down-regulated L-type Ca^{2+} channel [66].

ET Effects on Glucose Transport

In 1982, the increase in sensitivity of glucose transport process in skeletal muscle after ET was discovered. It was reported that ET could increase insulin sensitivity and moreover, it was shown that a session of swimming could lead to an increase in muscle glucose uptake in the absence of added insulin that could be measured in perfused rat muscle after cessation of ET [67]. These results were confirmed by Garetto et al. [68] in a study in which they showed that enhanced glucose uptake after ET occurred in two phases. The first phase is independent of added insulin and, as this increase in glucose transport was reversed, it was replaced by an increase in insulin sensitivity [68-70]. Subsequent studies have established that contractions can stimulate glucose transport in the complete absence of insulin [71-73] and that the maximal effects of contractions and insulin are additive in nature. Moreover, both contractions and insulin can stimulate glucose transport by separate signaling pathways. The initial steps in the signaling pathways by which contractions stimulate glucose transport have been identified in the heart [69]. One of these is the release of Ca^{2+} from the SR resulting in activation of Ca^{2+}/calmodulin-dependent protein kinase (CaMK) II, which is the isoform of CaMK found in skeletal muscle [74]. This process can be studied using sub-concentrations of agents such as caffeine, that release Ca^{2+} from the SR. Studies using this approach have shown that either the inhibition of Ca^{2+} release from the SR, or inhibition of CaMKII can prevent the increase in glucose transport induced by Ca^{2+} [69, 74].

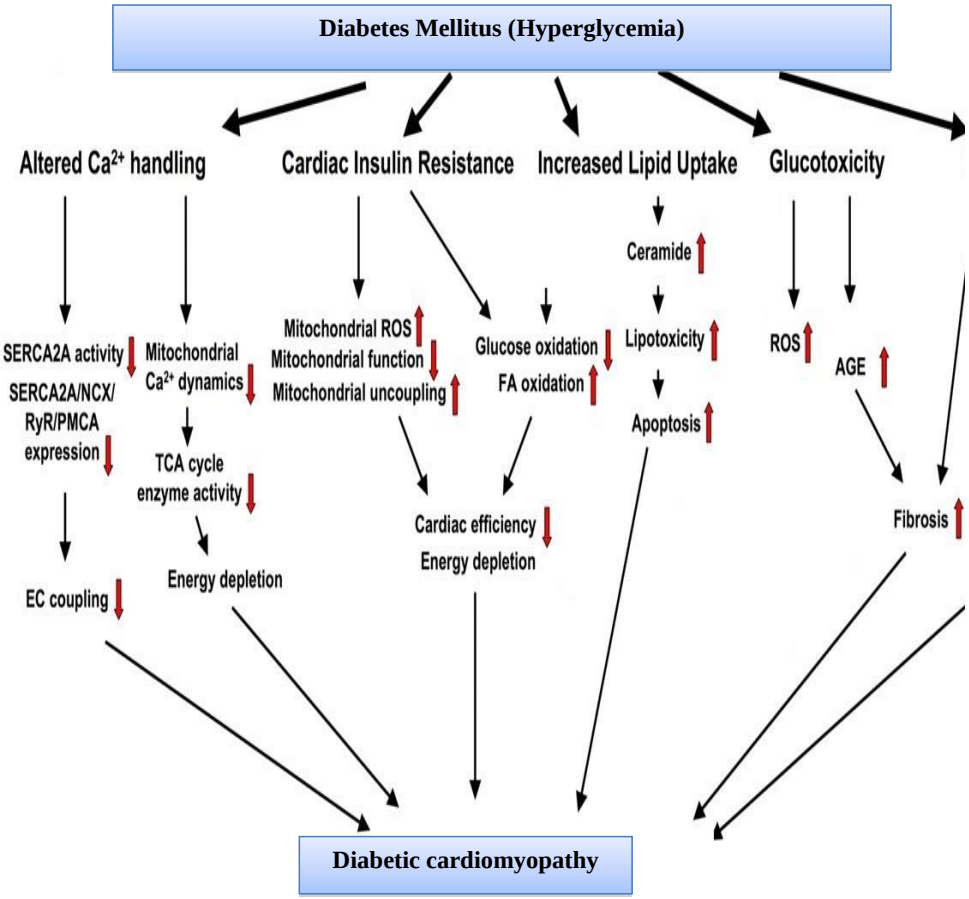

Figure 2. Flow diagram showing changes occurring in the heart during diabetic cardiomyopathy. DC can lead to structural, functional and biochemical changes at cellular and subcellular levels.

Athlete's Heart

In clinically healthy individuals, regular high-intensity physical activity for 5 to 6 hours per week may lead to cardiac adaptation known as an athlete's heart resulting in compensatory myocardial hypertrophy [75]. Acute responses to endurance ET include significant increases in maximum oxygen consumption, cardiac output, stroke volume and systolic blood pressure, all of which are associated with decreased peripheral vascular resistance. However, long-term cardiovascular adaptation to dynamic training results in increased maximal oxygen uptake due to increased cardiac output and arteriovenous oxygen difference. Strength exercise results in little or no increase in oxygen uptake. Thus, endurance exercise predominantly produces volume load on the left ventricle (LV), and strength exercise causes largely a pressure load [76]. LV physiological hypertrophy is caused by a proportional increase in myocardial cell length and width without evidence of myocardial hyperplasia in the majority of cases and this is mediated via increased cardiac insulin-like growth factor-1 (IGF-1) expression and activation of phophoinositide-3 kinase (PI3K) [77].

Physiological and pathological cardiac hypertrophies are caused by different stimuli and functionally distinguishable as illustrated in Table 1. A pathological stimulus causing pressure overload like aortic stenosis or hypertension produces an increase in systolic wall stress which results in in concentric hypertrophy (heart with thick wall relatively small cavities) [75]. However, pathological stimulus can cause volume overload resulting in aortic regurgitation or arteriovenous fistula. This produces an increase in diastolic wall stress resulting in eccentric hypertrophy

(heart with large dilated cavities and relatively thin wall). For the physiological hypertrophy, isotonic exercises such as walking, running and cycling involve movements of large muscles resulting in an increase in venous return and the increased volume will lead to eccentric hypertrophy. Generally, physiological concentric hypertrophy is caused by isometric or static exercise such as weight lifting which involves muscular tension against resistance with little movement. Reflex and mechanical changes rather than volume can cause a pressure load on the heart [78]. Function of the pathological hypertrophied heart may eventually decompensate leading to left ventricle dilation and heart failure, while in physiological hypertrophy, it does not decompensate compared to dilated cardiomyopathy of heart failure [75]. Thus, ET can result in a beneficial physiological, rather than an abnormal pathological growth.

ET-induced adaptation of the coronary circulation can be divided into two main processes. The first process is angiogenesis leading to an expansion of the capillary network by the formation of new blood vessels. This occurs at the level of capillaries and resistance arterioles, but not in large arteries. The second process involves arheriogenesis which can result in the enlargement of existing blood vessels [79].

The molecular mechanisms underlying angiogenesis induced by exercise training are not fully understood. It has been suggested that growth factors such as vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF) and angiopoietins (AQP), as well as their corresponding receptors, are involved in the process. In addition, proteases necessary for the degradation of the capillary basement membrane such as matrix metalloproteinases (MMPs), urokinase, tissue plasminogen activator and plasminogen, are also likely to contribute to the mechanism of sprouting angiogenesis [80].

Table 1: Table showing the changes which occur in the heart during ET and DC

Heart remodeling	Exercise Training	Diabetic Cardiomyopathy
Hypertrophy	Physiological hypertrophy does not decompensate to dilated cardiomyopathy of heart failure [75].	Pathological hypertrophy eventually decompensates leading to left ventricle dilation and heart failure [75].
Metabolism	Fatty acids and lactate are the major substrates for the heart during exercise [81]. Also increased rates of glucose oxidation and glycolysis [82]	Associated with reduced glucose and lactate metabolism, as well as increased fatty acid metabolism [38].
Oxidative stress	Decreasing reactive oxygen species (ROS) by dampening the activators of ROS producing enzymes [83].	Overproduction of reactive oxygen species (ROS) and reactive carbonyl species (RCS) [56].
Cellular Ca^{2+} homeostasis	Effectively restoring myocardial expression and activity of sarcoplasmic reticulum Ca^{2+} ATPase- pump (SERCA) [84].	Altering Ca^{2+} movement [60] by affecting the ability of SR to take up Ca^{2+}, and the Na^{+}-Ca^{2+} exchanger and the sarcolemma Ca^{2+} ATPase to extrude Ca^{2+} from the cell [61]

Non-Pharmacological Intervention for DC Treatment

The first recognition of ET as a non-pharmacological option to prevent and treat CVDs was in 1890s by Robert Babcock [85]. He stated that "Improved arterial circulation is so manifest a result of these exercises that lessen the frequency, nay, even the severity of attacks of angina pectoris in individuals with arteriosclerosis who had been unable to indulge in even very moderate physical exercise taken in the ordinary ways of walking." Currently, regular ET is a valuable therapeutic method/tool, and evidence from the scientific and medical communities strongly

supports the need to integrate the practice of regular ET in the therapeutic management of the disease and to limit diabetic-related long-term complications [86]. In fact, ET improves metabolic control and cardiovascular fitness. Many clinical studies have found that ET decreases cardiovascular risk factors [87, 88]. Similarly, several scientific reports have shown the advantages of ET on cardiac function and structure of diabetic patients, as well as in experimental models of DM, including reduced fibrosis, hypertrophy and apoptosis of the myocardium [89, 90]. Regular exercise is very important for maintenance of LV mass and function. As studied in bed-rest trials, prolonged physical inactivity leads to significant reductions in LV mass and impaired cardiac compliance, resulting in reduced upright stroke volume and orthostatic intolerance [91]. Since DC is associated cardiac remodeling (CR) which is characterized by myocardial hypertrophy, fibrosis and apoptosis, physiological hypertrophy in response to ET may differ in its structure and molecular profile to pathological hypertrophy [78].

The beneficial effect of exercise on coronary artery function has been demonstrated in diabetic rodent models [92, 93]. Since cardiac tissue has an extremely high metabolic demand, consequently, cardiac function is highly dependent on adequate coronary blood flow. Thus, coronary artery dysfunction directly impacts on optimal myocardial function. An eight-week moderate-intensity exercise regime in individuals with T2DM significantly improved endothelial cell function in the brachial artery as indicated by the improved flow-mediated dilation [94]. In another study, a 14-month moderate-intensity resistant training in adults with T2DM improved endothelial cell function-dependent and -independent vasodilation in response to acetylcholine and sodium nitroprusside, respectively [95]. Repeated exercise sessions may stimulate other adaptive changes which can contribute to both improved insulin sensitivity and metabolic health. Increased oxidative capacity and capillary density were observed in skeletal muscle in response to aerobic exercise [96]. In addition, increased adipose tissue insulin sensitivity has been observed 72-hours after completion of a 6-week exercise intervention [97].

ET Impact on Cardiac Metabolism in Health and During DC

Metabolic flexibility is the ability of the heart to ensure sufficient ATP production rate under diverse physiological and dietary conditions. The lack of this flexibility has been regarded as fundamental in the development of heart failure, including DC [98]. ET has an impact on cardiac metabolism. An acute exercise session can result in alteration of metabolic state by high level of plasma lactate from glycolysis in exercising muscle and non-esterified FAs. FAs and lactate are the major substrates for the heart during exercise [81]. In STZ diabetic rats, ET results in increased rates of glucose oxidation and glycolysis [82], while FA oxidation was unaltered [99].

ET and Oxidative Stress

It is now well established that increased ROS and RCS productions can lead to cardiac dysfunction by direct damage to regulatory proteins and DNA and induced apoptosis. Moreover, ROS producing enzymes are influenced by long-term endurance exercise training, through very different mechanisms. ET leads to improvement of insulin signaling, reduced inflammatory status, alteration of plasma lipids, and reduced RAS. Most likely, ET participates in decreasing ROS in the diabetic cardiomyocyte by dampening the activators of ROS-producing enzymes. It was reported that the exercise-induced elevation of mitochondrial ROS production was attenuated in cardiac mitochondria from endurance trained rats [83]. Theoretically, tissues with fewer cell divisions are more susceptible to cumulative damage by ROS compered to tissues with high replication rates [100]. One of the most frequently used bio-markers that provides an indication of the overall lipid peroxidation level is the plasma concentration of malondialdehyde (P-MDA), one of several byproducts of lipid peroxidation processes [78]. In animal models of ageing, increased malondialdehyde levels were observed in sedentary old rats. Although the expression of anti-oxidative enzymes such as superoxide dismutase (SOD) was unchanged, its enzymatic activity was reduced resulting in a net decline of anti-oxidative protection. Regular ET seems to delay the

accumulation of ROS-mediated cell damage by improving the anti-oxidative protection in the myocardium [100].

ET and Ca^{2+} Homeostasis

Calcium homeostasis has a major role in the process of contraction and relaxation (ECC) of the heart. ET has been shown to improve cardiac myocytes contractility in diabetic models and this improvement was associated with improvement of Ca^{2+} homeostasis. ET also prevents the development of DC and the dysregulation of SR protein content in an inducible animal model of T2DM [22]. Regular ET can effectively lead to restoring myocardial expression and activity of SERCA and L-type Ca^{2+}channel activity [84]. The release of Ca^{2+} from the internal SR via type 2 ryanodine receptor (RyR2) is an integral step in the cascade of events leading to cardiac muscle contraction [101, 102]. Recent studies showed that ventricular myocytes isolated from streptozotocin (STZ)-induced type 1 diabetic rat hearts exhibited increased frequency of spontaneous Ca^{2+} sparks. In longer term or more severe experimental diabetes, reduction in steady-state levels of RyR2 and other Ca^{2+} cycling proteins also contribute to the process [63, 103]. RyR2 becomes leaky during diabetes and this defect may be responsible for the reduced SR Ca^{2+} load. Diastolic Ca^{2+} release could also serve as a substrate for delayed after-depolarizations, contributing to the increased incidence of arrhythmias and sudden cardiac death in T1DM [102]. Alterations in the sensitivity of RyR2 to Ca^{2+} activation could result of oxidation in the RyR2 by either ROS or RCS [104]. Time to peak myocyte Ca^{2+} transient was prolonged by light and moderate exercise initiated 2 months after the onset of diabetes [105]. To date, the effect of ET during diabetes on myocyte intracellular Ca^{2+} cycling and the function of SR proteins remain poorly understood.

Psychological Intervention to Enhance ET Adherence

ET should be considered an essential therapeutic tool which has a beneficial effect on DC. In fact, the beneficial effects of ET have been observed to wane within 3 to 10 days or even longer following exercise. Therefore, effective ET therapy programs are associated with high ET adherence, as this would ensure long-term glycemic control [106].

Several factors create obstacles to ET, for example low motivational status, self-efficacy, negative learning history with exercising, lack of coping skills and aversive environmental characteristics such as reduced access to physical activity facilities, high costs of training programs, low social and cultural support and time barriers. Improving adherence to ET is a critical challenge. In order to promote adherence to ET, combined supplementary psychological intervention is extremely effective in encouraging the attendance to the exercise program [107]. In addition, national health services throughout the world should prescribe regular daily exercise to patients suffering from DC and other related diseases.

Conclusion

DM is a major metabolic disorder which can lead to damage and subsequent failure to a number of organs in the body including the heart where hemodynamic disturbances frequently occur. Figure 2 summaries the processes and mechanism(s) whereby DM can lead to DCM subsequently and heart failure. Initially, these are induced at sub-cellular, cellular, molecular and interstitial levels in the heart, including changes in size, shape and function of the myocardium. Diabetes, if left untreated, can result in hyperglycemia-induced generation of ROS and RCS, endothelial and mitochondrial dysfunctions, structural changes to cardiomyocytes, infiltration of fibrosis, apoptosis or death of some cardiomyocytes, followed by hypertrophy, disturbances in cellular calcium homeostasis, myofilaments insensitivity to calcium and subsequently delayed contraction and prolonged relaxation all leading to remodeling of the myocardium. Most of these changes in the heart can either be delayed or prevented by regular ET, which is a valuable non-pharmacological therapeutic tool. It is now highly recommended by scientific and medical communities, which strongly support the need to integrate the practice of regular ET in the therapeutic management of the disease and to limit diabetic-related complications. Of particular importance, ET can also

improve metabolic control and cardiovascular fitness. Many clinical studies have found that ET decreases cardiovascular risk factors. However, the cellular and molecular mechanisms underlying DC and heart failure in diabetes are not fully clear and further studies should be done to unravel the process.

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