

Cardiac and Metabolic Consequences of Aerobic Exercise Training in Experimental Diabetes

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Abstract: The experimental literature of the foregoing decade has furnished an assemblage of mechanisms explaining the metabolic perturbations and overall decline in cardiac performance implicated in the pathogenesis of diabetes mellitus. Particularly, the experimentally-induced diabetic rat model has been indispensable in the examination of diabetic cardiomyopathy, an entity distinctly separable from atherosclerosis, hypertension, coronary artery disease and valvular dysfunction, yet convincingly attributable to the increase in cardiac-associated mortality commonly observed in the diabetic patient. The widespread epidemic of diabetes mellitus in developed societies has elicited considerable attention and the role of exercise as an adjuvant therapy in diabetes management has been increasingly emphasized. However, the evidence endorsing the beneficial attributes of exercise in the diabetic state is indeterminate despite markedly observed increases in myocardial and skeletal muscle glucose homeostasis, endothelial and autonomic function, insulin sensitivity and amelioration of diabetes pathogenesis. As evidenced by review of the experimental literature, a mild to moderately intense exercise regime may be a reliably implicated insulin-sensitizing therapy for the experimentally-diabetic rat model as well as the human diabetic patient. Notably, the cardio-protective and metabolic benefits of aerobic exercise are seemingly more pronounced in those individuals most susceptible to diabetes progression.

Keywords: Diabetes, Streptozotocin, Exercise, GLUT, Cardiac, Metabolism.

1. INTRODUCTION

Experimental diabetes in the rodent is associated with an array of metabolic aberrations analogous to human diabetes mellitus, the most common endocrine disorder in developed countries [1]. Induction of diabetes mellitus in the rat using streptozotocin (STZ), a toxin that selectively destroys islet β -cells, is marked by hypoinsulinemia, hyperglucagonemia with subsequent hyperglycemia [2,3]. Also noted in this model of diabetes is a reduction in body weight, altered lipid profile, decrease in physical activity, and depression in left ventricular performance [2-4]. Rats with STZ-diabetes mellitus subjected to regular exercise training regimes have previously demonstrated notable improvements in glucose homeostasis and increased cardiac performance [5-9]. Likewise in humans, the outcomes of a standardized exercise regime include reduction of blood glucose, blood pressure, body weight, body fat, and more specifically mobilization of abdominal and visceral adipose tissue, increased insulin sensitivity, improvement of atherogenic lipoprotein profile and inflammatory elements [10,11]. Surprisingly, type 2 diabetic and obese patients who habitually exercise, even in the absence of weight loss, may substantially reduce total and visceral fat and skeletal muscle lipid content [12]. Although physical training has been reliably implicated in improving myocardial function and metabolic homeostasis the mechanisms whereby effector functions occur are yet to be fully elucidated.

The overwhelming majority of diabetes cases comprise the type 2 diabetes phenotype, characterized by a progressive

deterioration in insulin-mediated glucose uptake in peripheral skeletal muscle tissue and disturbances in fatty acid metabolism [13]. Particularly concerning is the predicted two-fold increase in the incidence of diabetes within the population over the upcoming decades including an escalating rise in type 2 diabetes in adolescents attributable to an increasingly sedentary lifestyle and a marked rise in pre-diabetic and coronary heart disease risk factors [1,10,14]. Additionally, metabolic syndrome with its associations, namely obesity, dyslipidemia, hypertension, atherosclerosis, and whole-body insulin resistance is convincingly most notable [1,10,14,15]. Traditionally, pharmaceutical therapeutics has been implicated for glycemic control in type 2 diabetic patients. However, the detrimental long-term consequences of drug therapy have spurred the investigation of aerobic exercise as an alternate insulin sensitizer [14]. Furthermore, aerobic exercise has gained increasing popularity as a multidisciplinary approach to diabetic therapy although some contraindications have been recognized [10,16]. **The benefits of exercise for the diabetic population are illustrated in Fig. (1).** Individuals with impaired glucose tolerance, a recognized antecedent to overt type 2 diabetes, have been characterized as sedentary, poorly physically fit and insulin resistant. Exercise within this population has been strongly recommended as a preventative lifestyle measure to intercept disease development [17]. Collectively, the outcomes of clinical trials strongly associate the prevention or delay of type 2 diabetes by lifestyle interventions including weight loss and habitual exercise [1,18]. **In experimental studies, however, critical examination of the literature revealed that the STZ model of diabetes mellitus remains the model of choice to investigate the exercise-mediated physiological adaptations in the heart and skeletal muscle. Table 1 shows the common**

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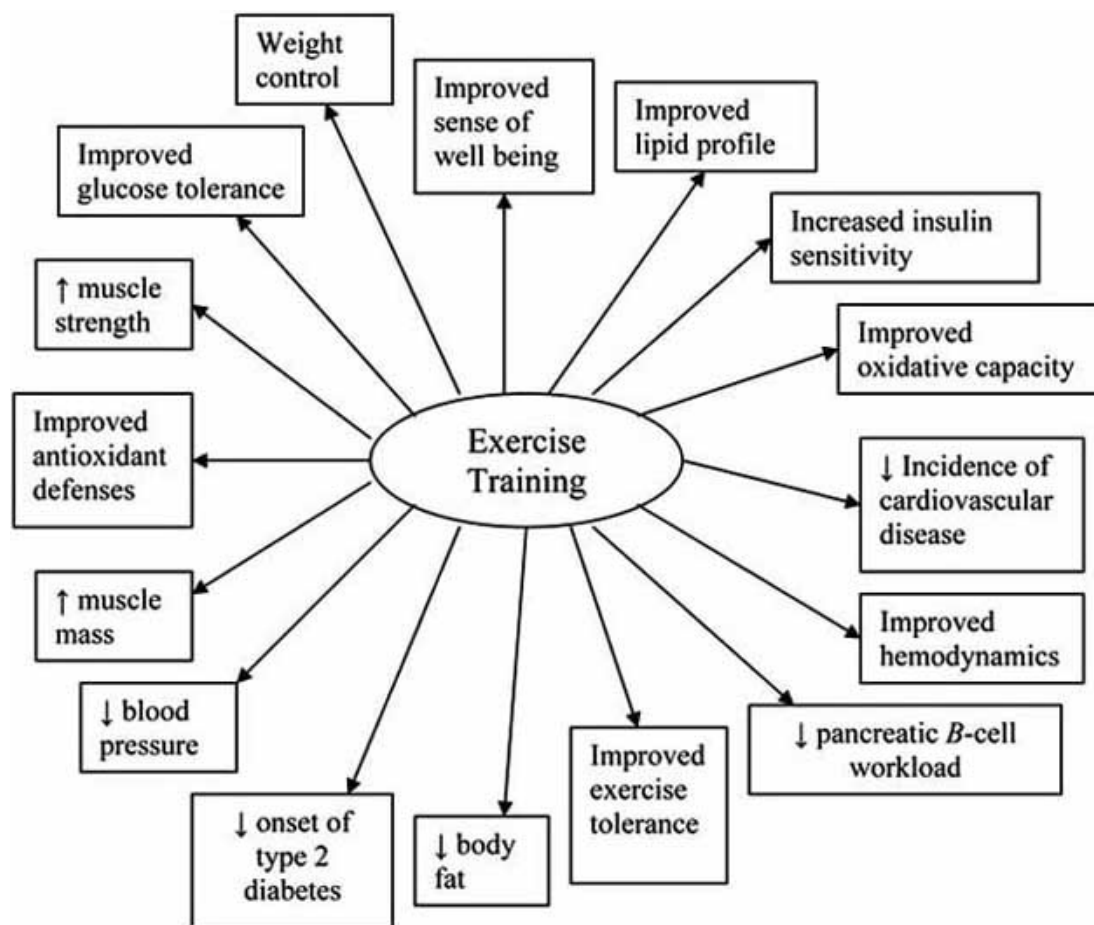


Fig. (1). Beneficial effects of exercise for the diabetic patient.

diabetic rat models used in exercise training studies. In this regard the proceedings of this review are noteworthy.

2. IMPACT OF EXERCISE TRAINING ON GLUCOSE HOMEOSTASIS

The impact of exercise training on glucose homeostasis in skeletal muscle of STZ-diabetic rats has been attributed to the following mechanisms; increase in GLUT4 content, a protein found in intracellular vesicles and is translocated to the plasma membrane in response to insulin and exercise, increase in insulin-mediated glucose uptake, and a two-fold enhanced capacity of the pyruvate dehydrogenase complex (PDH) activity, the rate limiting enzyme of aerobic glucose oxidation in tissue [19]. Pold *et al.* have described an increased GLUT4 protein expression in exercised skeletal muscle and subsequent increase in whole body insulin sensitivity in the ZDF rat, a model that closely resembles human type 2 diabetes [20]. This represents a training effect that restores PDH activity and glucose metabolism, a pathway that is typically reduced in diabetes (Fig. 2) [7]. Physical training in the absence of insulin may increase glucose uptake in chronically contracting skeletal muscle and thereby independently activate PDH complex activity [19]. Activated protein kinase C (PKC- δ) *in vitro* has been implicated in insulin-mediated glucose transport by translocation of GLUT-4 to the plasma membrane of rat skeletal muscle tissue. Enhanced PKC- δ activation in the *Psammomys obesus* (sand rat) model of nutritionally-induced

insulin resistance and type 2 diabetes mellitus following exercise training has been described by Heled *et al.* in its relation to disease retardation [21]. Although the precise regulatory mechanisms between exercise-mediated increase of PKC- δ activity and GLUT-4 translocation to surface membranes are currently undefined, this relationship may warrant future inquiry. AMPK, particularly sensitive to fluctuations in AMP-to-ATP balance, has been recognized a regulator of glucose and lipid metabolism during exercise. Recurrent activation of AMP-activated protein kinase post-exercise with peripherally enhanced insulin sensitivity and preservation of β -cell function has been implicated [20]. Upon histological exam, Shima *et al.* have reported markedly enlarged and fibrotic pancreatic islet cells of sedentary OLETF rats, a type 2 model of diabetes, compared to their trained counterparts which demonstrated preserved pancreatic function. These findings exemplify a compensatory response to insulin resistance, wherefrom the islets increase insulin secretion, the β -cells exhaust then perish, and fibrotic tissue infiltrates [22]. The progression of frank diabetes may be altered in the pre-diabetic insulin-resistant state by exercise-mediated increased peripheral insulin sensitivity in skeletal muscles and diminishment of pancreatic β -cell workload [20]. However, in resemblance to human type 1 diabetes, the BB/Wor rat model has been studied particularly as pancreatic β -cell destruction is provoked by lymphocytic insulinitis [23]. Whether exercise training confers protection against autoimmune pathogenesis of type 1 diabetes has been

Table 1. Characteristic Features of Common Diabetic Rat Models Used in Exercise Studies

| Model | Major Features | Key References |
|----------------------------|---|---------------------------------------|
| Type 1 diabetes | | |
| Streptozotocin | Chemically-induced; acute destruction of pancreatic β -cells. Insulinopenia, hyperglycemia, ketonemia, glucosuria, weight loss, ketoacidosis [†] | [7-9, 19, 24, 26, 28, 30, 40, 42, 55] |
| BB Wor | Spontaneous autoimmune insulinitis and lymphocytic infiltration. Insulinopenia, hyperglycemia, ketonemia, glucosuria, weight loss, ketoacidosis | [23, 44] |
| Type 2 diabetes | | |
| JCR:LA | Spontaneous development of type 2 diabetes. Obesity, insulin resistance, hyperinsulinemia, hyperglycemia, hypertriglyceridemia, hypercholesterolemia, atherosclerosis | [38] |
| OLETF | Spontaneous development of type 2 diabetes. Mild obesity, insulin resistance, hyperinsulinemia, hyperglycemia, hypertriglyceridemia | [22] |
| Sand rat & Sucrose-feeding | Nutritionally-induced Mild obesity, insulin resistance, hyperinsulinemia, hyperglycemia, hypertriglyceridemia | [21, 37] |
| ZDF | Spontaneous development of type 2 diabetes. Obesity, insulin resistance, hyperinsulinemia, hyperglycemia, hypertriglyceridemia, hypercholesterolemia | [20] |

disputable. Studies by Noble *et al.* failed to substantiate any beneficial impact of physical training on preservation of β -cell integrity and autoimmune insult [23]. The consequences of aerobic exercise training however, on the delayed or reversible progression of type 2 diabetes has been more extensively categorized.

Whether exercise training enhances glucose tolerance and insulin sensitivity in skeletal muscle of severely diabetic rats has been highly debatable as contradictory models have been presented [24]. Proposed mechanisms whereby training-induced improvements in the severely diabetic state occur have been presumptively attributed to an enhanced insulin secretory capacity, significant decrease in hyperglycemia and subsequent β -cell replication stimuli, favorable alteration of plasma lipid profiles and increased insulin sensitivity thereby collectively improving glucose utilization [5,10]. Riggs *et al.* have observed that STZ-diabetic trained rats exhibited increased insulin sensitivity, despite notably reduced serum insulin levels, or an increase in non-insulin mediated glucose transport [6]. Severely diabetic rats subjected to a moderate exercise training expressed significantly higher basal insulin levels than their sedentary counterparts as well as decreased basal glucose levels [5]. A reduced hyperglycemic state attenuates the progressive metabolic deterioration of diabetes by preservation of islet cell function and enhanced glucose transport [5,25]. However, these observations were transiently noted in studies conducted by Rousseau-Migneron *et al.*, as typically-expected insulin levels resumed after 9 days of detraining suggestive of a more acutely adaptive response [5]. Contrarily, Goodyear *et al.* have indicated that exercise

training may substantially impact glucose-intolerant and mildly diabetic animals but insufficiently alters these parameters in severely diabetic counterparts [24]. Furthermore, highly intense exercise regimes may be less conducive to the reduction of hyperglycemia, oral glucose tolerance or skeletal muscle glucose uptake in severely diabetic states [24,26]. Despite the apparent inconsistencies on the benefits of exercise in severe diabetic states, it may be noted that physical training does not seemingly appear to worsen any diabetic-related condition with the noted exceptions of human diabetic subjects with cardiac autonomic neuropathy and STZ-diabetic rats exercising above 90% VO_2 max [16,24,27]. Additionally, high intensity training in the STZ-rat does not appear to confer more protection against ischemic injury compared to moderate training [28]. Nevertheless, aerobic exercise of moderate or mild-intensity has been preferentially described for diabetic patients and likewise permeates the experimental literature as an indicated therapy for diabetic rats [10,17].

3. AEROBIC EXERCISE ON MYOCARDIAL GLUCOSE TRANSPORT CAPACITY

STZ-induced diabetes is linked to a substantial decline in glucose transport activity in cardiac sarcolemmal vesicles mediated by a decrease in sarcolemmal surface glucose transporter proteins (GLUT), total membrane GLUT-4 protein extract, and GLUT-4 mRNA [29-31]. GLUT-4 protein corresponds to the capacity for glucose utilization in insulin-dependent tissues and impairment of myocardial glucose transport is critical during episodes of ischemia or increased workload when glucose demand exceeds transport capacity

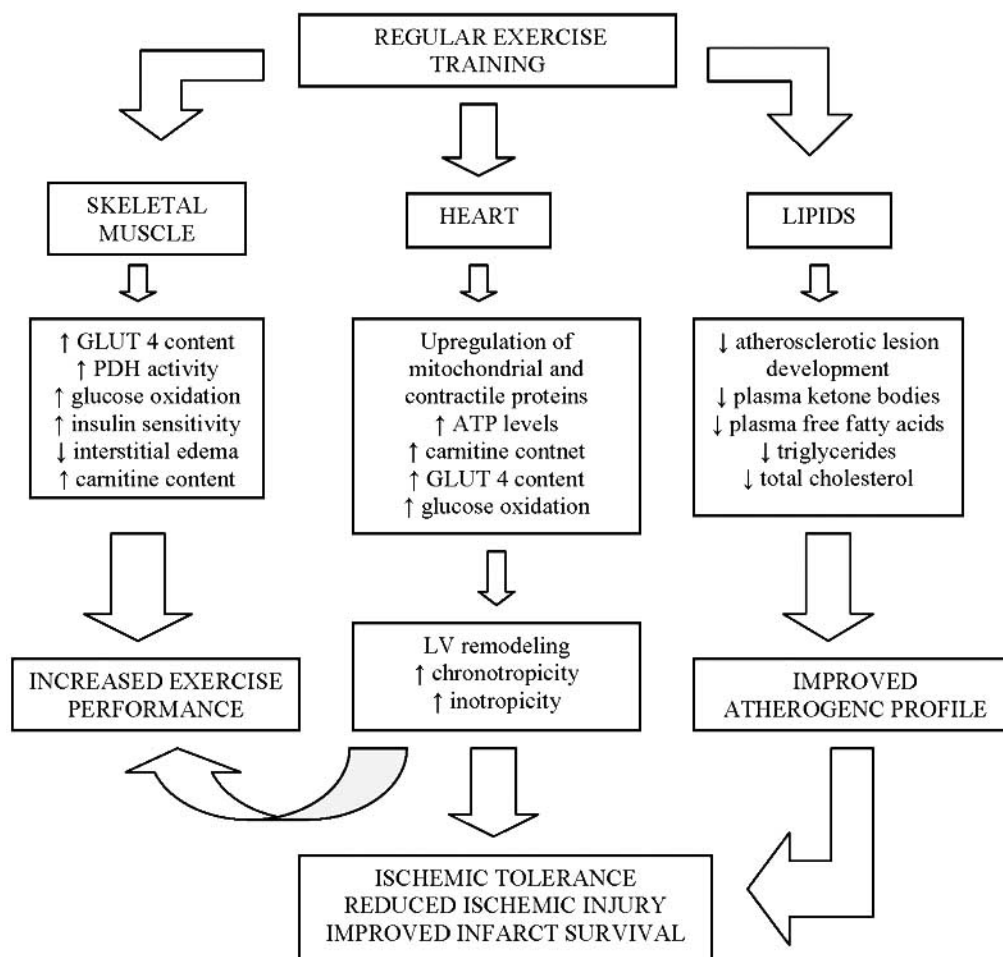


Fig. (2). Beneficial effect of regular exercise training in the STZ model of diabetes.

[30]. Physical training has been investigated in a potentially restorative role by attenuating the diabetes-induced reduction of glucose transporters and may provide a robust stimulus for increased glucose uptake in peripherally deficient tissues as commonly associated with diabetes [30,32]. Osborn *et al.* have proposed that an increase in myocardial sarcolemmal GLUT-4 and mRNA levels in diabetic myocardium may enhance cardiac function and myocardial glucose oxidation (Fig. 2) [29]. The metabolic cascade responsible for the observed effect of exercise training on myocardial GLUT-4 expression is currently unidentified. Adenosine, a suggested mediator, released under conditions of exercise, ischemia, increased workloads and enhanced contractile activity, has been indicated in the translocation of GLUT-4 transporters [32,33]. Additionally proposed regulators of GLUT-4 translocation are 5'AMP-activated protein kinase and nitric oxide [32]. Hall *et al.* have reported a substantial increase in myocardial GLUT-4 levels in moderately exercise-trained diabetic rats compared to their sedentary counterparts, a relationship inversely related to fasting blood glucose concentrations [30]. Such findings may link the prevailing blood glucose with myocardial GLUT-4 protein regulation and increased capacity of the heart to utilize glucose [30].

Bradykinin, also released in response to contracting muscle during exercise may be another candidate involved in modulating exercise-induced glucose transport and subsequent reduction of plasma glucose levels by an insulin-independent increase in GLUT-4 translocation [32]. The increase of plasma bradykinin associated with bouts of exercise was exclusively related to diabetic patients and rats with reasonable glycemic control in studies conducted by Taguchi *et al.* [32].

Undergoing analogous changes with exercise are diaphragmatic modifications described by Ianuzzo *et al.* [34]. The diaphragm, a peculiar skeletal muscle has been likened to the myocardium by its chronically active nature and its unique consideration as a vital organ. The diaphragm muscle of the chronic STZ-diabetic rat typically exhibits depressed glycolytic capacity as a result of increased free fatty acid availability from β -oxidation capacity and reduced glucose utilization [34]. Exercise-induced modifications of diaphragmatic enzyme profiles, particularly hexokinase and phosphofructokinase have been observed to enhance glycolytic capacity. Further supporting the benefits on carbohydrate metabolism is the reduction in blood lactate levels seen after exercise training. Sedentary diabetic rats

exhibit a measurable elevation of blood lactate concentrations which is attributed to a reduction in monocarboxylate transporter proteins found in heart and skeletal muscle. Exercise training induced a reduction of plasma glucose levels and upregulation of monocarboxylate transporter proteins in these tissues, an effect that may be partly responsible in the normalization of lactate levels observed in trained diabetic animals [35].

4. EXERCISE, CARDIAC FUNCTION, AND TOLERANCE TO ISCHEMIA

Diabetic cardiomyopathy is distinctly separate from typical macro- and micro-vascular diseases, including atherosclerosis, hypertension, coronary artery disease and valvular dysfunction [10]. Its hallmarks, aberrant intracellular calcium (Ca^{2+}) homeostasis and alterations in energy metabolism, are directly contributory to myogenic cardiac abnormalities associated with diabetic disease progression [10]. Impaired Ca^{2+} metabolism following the induction of diabetes has impelled aberrant contractile functioning. Particularly altered Ca^{2+} uptake by the sarcoplasmic reticulum (SR) with concomitant depression of SR Ca^{2+} -ATPase function, have been denoted [36].

Davidoff *et al.* have detailed the preventable and reversible nature of cardiomyocyte dysfunction in the sucrose-induced model of insulin resistance [37]. The development of overt type 2 diabetes induced in sucrose-fed animals leads to whole body insulin resistance and cardiac compensatory prelude to overt disease [37]. To date, most animal models resemble moderate to severe end stage type 2 diabetes mellitus. In this regard, the findings of Davidoff *et al.* are noteworthy, particularly as the early pathogenesis of diabetic cardiomyocyte dysfunction is reversibly altered by exercise intervention [37]. Indeed altered cardiomyocyte mechanical properties, expressed as contraction, time to peak twitch, and relaxation, can be prevented in insulin-resistant rats with prior exercise. Diminishment of left ventricular end-diastolic chamber and myocardial wall compliance are early hallmarks of diabetic cardiomyopathy [26]. Irreversibly glycation myocardial collagen with enhanced tensile strength may be attributable to the observed myocardial stiffness. Woodiness *et al.* have associated an exercise-induced decrement of myocardial stiffness independent of alterations in advanced glycation end products of myocardial proteins [26]. Distinctly attributable to rats is their relative resistance to atherosclerosis development which evidently is clearly not the case in human diabetic patients. However, in the JCR corplent rat model of relevant atherosclerosis, obesity, very low-density lipoprotein hyperlipidemia and insulin resistance, intensive aerobic exercise resulted in a substantial decline in myocardial atherosclerotic lesion development [38].

Clinical and experimental evidence also indicate the reduction in glucose uptake and subsequent decrease in myocardial glucose utilization as determinants in diabetic cardiomyopathy [7]. Altered myocardial metabolism, particularly glucose oxidative capacity, has been coupled to a decreased rate of spontaneously beating atria in STZ-rats [36]. The role of altered glucose metabolism in diabetic cardiomyopathy is supported by the observations in which pharmacological stimulation of PDH activity improves the chronotropic and

inotropic state of the heart [39]. Paulson *et al.* [40] were the first to report that rates of myocardial glucose oxidation were increased in the STZ-diabetic rat heart. A study from our laboratory later confirmed this effect and further demonstrated that glucose oxidation was also increased in STZ-diabetic hearts following ischemia [7]. Myocardial glycolysis was increased as well in hearts during the ischemic period, a mechanism that is protective against ischemic injury by providing an additional source of energy to the recovering heart.

Nadeau *et al.* have associated chronic STZ-diabetes with an increased death rate following acute coronary artery ligation, a model designed to resemble the increased mortality rate observed in human diabetic patients following an acute myocardial infarct [41]. Further inferred in this model of acute myocardial infarct in the STZ-rat heart, acute metabolic disturbances may be influential in the observed increased mortality as rats dying within the first 20 minutes had higher plasma glucose concentrations and a reduction in insulin levels. The initial 20 minutes proceeding acute coronary artery ligation have been characterized as a preeminent period for sudden death [42]. However, their presupposition was subsequently remodeled as later studies revealed no apparent acute metabolic disturbances at the time of myocardial infarct. Pertinent parameters, namely lower basal plasma insulin levels and an acute increase in free plasma carnitine levels, were observed in rats surviving more than 20 minutes post myocardial infarct and potentially warrant further investigation. These findings imply that long-term diabetic consequences and not acute metabolic disequilibrium responsibly define myocardial infarct survival [43]. Later studies thereafter revealed that exercise training prior to the onset of diabetes may improve the early survival rate of diabetic rats submitted to experimental myocardial infarct independently of glucose homeostasis [42]. However, acute disturbances in the metabolic status of type 1 diabetic rats resulting from insulin withdrawal and accumulation of plasma free fatty acids, accelerates ischemic heart failure in sedentary diabetic rats [44].

The hearts of endurance trained STZ-diabetic rats seemingly demonstrate enhanced protection against ischemia, particularly as evidenced by reduced mortality, greater post-ischemic recovery and preservation of left ventricular function such as heart rate, aortic flow, coronary flow as well as diminishment in the severity of myocardial ischemia (Fig. 2) [6-9, 28, 42, 44]. Protection against ischemic heart failure in response to exercise can even occur regardless of metabolic control [44]. Although clinical studies have affirmed a high susceptibility of the diabetic heart to post-ischemic injury and cardiac dysfunction following myocardial infarction, the evidence presented in experimental literature is debatable. Myocardial response to ischemic events has been presented by Riggs *et al.* whereby exercise training did not favorably impact a 30-minute period of induced myocardial ischemia [6]. Contrarily, we have observed an increased tolerance to 60-minutes of low-flow ischemia in trained STZ-diabetic hearts [7]. Paulson *et al.* have studied the vulnerability of STZ-diabetic rat hearts to a 75-minute period of global ischemia proceeded by 30 minutes of reperfusion. Their studies affirm that induced global ischemia detrimentally impacted recovery of coronary flow, cardiac output

and aortic systolic pressure in sedentary diabetic rats compared to their physically trained counterparts. Decreased susceptibility to ischemia was exclusively observed in trained diabetic animals, implicative of a more pronounced exercise-induced advantage in this diseased population [9]. The reasons for these discrepancies are not known, but may relate to the differences in the ischemic model used, the degree of coronary flow during ischemia and to the inherent alterations in glucose use in the heart determined by the severity of the diabetic state. Indeed, supporting the latter, the reduction in glucose use by the heart can be partially reversed by exercise [7,30,40]. Concordantly, several large prospective human studies have likewise revealed the protective benefits of physical training are markedly pronounced in those individuals most susceptible to disease development [45]. In the studies described above [7,8,9,44], hearts from trained non-diabetic animals rats failed to demonstrate an increased tolerance to ischemic stress. A reasonable explanation is that exercise outcomes are intensity-related and bear particular impact on animals with substandard functional status and may not equivocally apply to milder or absent disease states.

5. EXERCISE AND UPREGULATION OF MITOCHONDRIAL AND CONTRACTILE PROTEINS

Sylvestre-Gervais *et al.* have associated diabetes mellitus with diminished protein synthesis in the heart, observable in decreased protein content in cardiac membranous preparations [46]. Furthermore, exercise training up-regulated protein synthesis in diabetic animals. Whether physical training intensifies insulin-mediated production of enzymatic machinery for mitochondrial protein synthesis is suggested. Elevated mitochondrial enzymes may subsequently enhance energy metabolism, particularly mitochondrial oxidative phosphorylation [47]. In support of this speculation, Mokhtar *et al.* have investigated the diminished mitochondrial oxidative capacity of glutamate and decline in energy production in chronically STZ-diabetic rats. Their studies have revealed a physical training related increase in phosphocreatine (PC) and ATP levels in the myocardium of diabetic rats with an improvement in mitochondrial function, expressed as state 3 respiration and ATP production. More substantially, these studies have supported that altered mitochondrial function of chronically diabetic rats may be reversible with an endurance training regime, an observation independent of glucose homeostasis [47]. Related studies have indicated that the diminution in PC levels in the hearts of chronically diabetic rats may be modified by endurance training [48]. Myocardial energy utilization deficit and subsequent decline in cardiac metabolism was investigated by Mokhtar *et al.* whereby a diminution in creatine kinase (CK) has been reported in rats with STZ-diabetes. Furthermore, insulin deficiency has been implicated in the decreased synthesis of the CK protein and physical training may modify this effect. Physical conditioning has been reported to substantially alter the repression of cardiac performance in the diabetic rat heart by increasing mitochondrial CK isoenzyme activity and CK-MB (myocardium isoenzyme) and thereby increasing the efficiency of high-energy phosphate transfer within the cell [49]. Nadeau *et al.* have likewise observed a significant decrease in plasma CK-MB isoenzyme in chronically diabetic rats and have attributed

this consequence to persistent diabetic myocardial alterations [43].

In vivo investigations of diabetic dyslipidemic pigs, a proposed parallel model to human diabetic cardiomyopathy, have revealed significant alterations in cardiac myofibrillar proteins, namely decreased baseline levels of cAMP-dependent protein kinase-induced phosphorylation of troponin I and myosin-binding protein C in addition to impairment of myocardial function [50]. Myocardial dysfunction marked by decreased rates of pressure development and depressed left ventricle fractional shortening has been described. Consequently, improved myocardial function, altered cardiac troponin T isoform composition and covalent modification of myofibrils have been independently attributable to the direct impact of endurance exercise-training on the myocardium [50]. Ventricular heavy chain myosin (MHC) isoforms are prevalent in three enzymatic conformations in rat cardiac tissue. Two isoforms have been particularly examined in relation to exercise-induced isoform shifting in the diabetic state. The α -MHC isoform predominates in healthy cardiac tissue of normal rats and exhibits the most efficient ATPase activity whereas the β -MHC isoform exhibits less efficient ATPase activity and predominates in cardiac tissue of diabetic rats [51]. Paulson *et al.* have concluded that the beneficial effects of exercise on protein composition in diabetic cardiac tissue did not induce a normalization of cardiac myosin isoenzyme expression [51]. The observed isoform switch, α -MHC to β -MHC, may reflect compensatory measures to maximize energy metabolism at a lower threshold.

6. ROLE OF EXERCISE ON OXIDATIVE STRESS IN DIABETES

Although atherogenesis in humans has historically been attributed to dyslipidemia, convincingly, oxidative stress, inflammation, endothelial cell and platelet activation, and plaque stability are jointly contributable [15]. Disruption of endogenous tissue defense mechanisms and heightened susceptibility of stress-induced tissue damage have been associated with diabetes [36,52]. Chakraphan *et al.* have attributed STZ-diabetic cardiovascular perturbations to endothelial dysfunction, namely increased leukocyte adhesion, over-expression of adhesive molecules and impairment of endothelium-dependent vasorelaxation [53]. A hyperglycemic state also augments the heightened production of reactive oxygen species (ROS) and subsequently impedes vasoactive nitric oxide formation. Moreover, altered endothelial-dependent relaxation may relate to increased production of vasoconstrictor prostaglandins in diabetes [36]. Routine low intensity exercise may observably equilibrate the oxidative and anti-oxidation system, thereby counterbalancing deleterious endothelial dysfunction [53]. Protein oxidation, a derivative of oxidative stress in STZ-diabetic animals consequently incites an inflammatory cascade, typically presented by interstitial edema in skeletal muscle and lymphocyte infiltration in the heart [52]. However, endurance training may attenuate STZ-induced cardiac inflammation while upregulating tissue heat shock protein expression, an endogenous antioxidant defense presumably depressed in diabetes [52]. Human studies have concurrently submitted an exercise-mediated amelioration in endothelial

dysfunction by means of nitric oxide production, decreased nitric oxide scavenging and ROS production [15].

7. LIPID AND KETONE METABOLISM IN THE EXERCISE-TRAINED DIABETIC RAT

In STZ-induced insulinopenia, the inability to metabolize carbohydrate fuel sources compels tissues to utilize ketone bodies and lipids thereby depleting fat stores and inducing weight loss [2]. The development of moderate hyperketonemia, particularly the accumulation of acetoacetate, has been described in diabetic rats proceeding prolonged exercise. Comparably this phenomenon has been observed in humans both diabetic and healthy. In spite of this, Ohmori *et al.* have strongly correlated habitual exercise with the marked reduction of plasma ketone bodies and glucagon in mildly diabetic rats and plasma ketone bodies, particularly acetoacetate, in severely diabetic rats [54]. Upregulation of the hepatic ketone body synthesis pathway is induced in diabetes, and as expected, chronic insulin deficiency in rats accordingly yields a substantial increase in both plasma free fatty acids and β -hydroxybutyric acid concentrations [55]. In a series of studies by Midaoui *et al.* [55,56], plasma concentrations of β -hydroxybutyric acid in diabetic rats may be reduced with physical training despite any notable changes in plasma glucose or insulin levels. This exercise-incited reduction in circulating concentrations of ketone bodies has been attributed to decreased production in the liver or increased uptake by peripheral tissues. This enhanced capacity to utilize ketone bodies may be partly mediated by the action of 3-ketoacid CoA-transferase in skeletal muscle and the subsequent decrease of β -hydroxybutyric acid levels, a mechanism seemingly defective in sedentary diabetic rats [56]. Alternatively, physical training of diabetic rats depresses HMG-CoA synthase, a rate-limiting enzyme in hepatic ketogenesis [55]. Exercise training of diabetic rats has also demonstrated significant reduction in plasma free fatty acid, triglyceride concentrations, total cholesterol, and high-density lipoprotein with resting blood glucose concentrations remaining virtually unaltered [1,24,40,57].

Carnitine is an essential cofactor in the transfer and oxidation of fatty acids in the mitochondria of highly oxidative tissues such as heart and skeletal muscle. Carnitine metabolism is altered in STZ-diabetes as decreases in plasma carnitine levels and free carnitine content of the heart and other tissues have been reported [8,58]. Exercise training has been reliably implicated in the preservation in carnitine levels in the hearts of diabetic rats [8,40]. Proceeding synthesis in the liver, carnitine is released into the circulation wherefrom it is taken up by oxidative tissues to facilitate energy metabolism. Decreased peripheral carnitine uptake has been implicated in dysregulation of glucose and fatty acid oxidation [8,39]. Disturbances in fatty acid oxidation have been reported to increase the likelihood of cardiac ischemic insult in the insulin-treated, poorly controlled diabetic and in the STZ-diabetic rat heart [44]. Exaggerated fatty acid metabolism and decreased carnitine content may impede cardiac contractility by interruption of glucose homeostasis [39]. Intervention aimed at lipid reduction or inhibition of fatty acid uptake or oxidation prevents ventricular dysfunction and improves glucose metabolism in the reper-fused heart model [7]. Paulson *et al.* have studied the

hypolipidemic outcomes attributable to exercise training and demonstrated that the capacity for the diabetic heart to oxidized glucose as energy substrate is increased [40]. This is consistent with concept that intervention or therapy aimed at decreasing circulating lipid levels resulting in greater glucose use by the heart [39].

8. ADRENERGIC COMPENSATORY ADAPTATIONS TO EXERCISE-TRAINING IN THE DIABETIC STATE

In addition to alterations in Ca^{2+} and glucose metabolism, dysfunctional intrinsic electrical and contractile properties as well as myocardial adrenergic receptor and cholinergic receptor populations are contributing factors to impairment in left ventricular function in diabetic rats. [36]. Exercise-induced modification of the adrenergic system has been proposed to elevate insulin sensitivity in experimental diabetic rats [59]. Highly intense exercise bouts have been ascribed to increasing glucose uptake in contracting skeletal muscle 7 to 20 times over the basal level [17]. The physiological stressors derived from sufficiently intense exercise regimes have been described to activate adaptive mechanisms within the sympathoadrenal system, including increased epinephrine secretion [60]. Peculiarly however, intense exercise provokes the release of counter regulatory hormones, namely glucagon and catecholamines, which blunt the efficacy of insulin [17]. The adrenergic adaptive mechanisms to exercise whereby this effect is overcome particularly in the diabetic state have been examined. Jobidon *et al.* have demonstrated that basal plasma levels of epinephrine in normal and diabetic rats, endurance trained by a standard 10-week treadmill running program exhibited a two-fold increase in catecholamine levels compared to their sedentary counterparts [59]. In contrast to these findings, Nadeau *et al.* have reported no evident training-induced adaptation of the sympathetic nervous system in experimental diabetes mellitus. To further this supposition, Jean *et al.* have described that the enhancement of insulin sensitivity induced by physical training is not mediated by an increase in epinephrine secretion from the adrenal medullae. In further support of this notion, peripheral glucose utilization was not seemingly altered by adrenal demedullation [60]. Treadmill running does not seemingly influence the basal norepinephrine turnover in heart, liver, pancreas, and gastrocnemius muscles in the rat as reported by Nadeau *et al.* [61]. Chronically-elevated exercise-induced catecholamine levels have been associated with a down-regulation of β -adrenergic receptors and subsequent decline in sympathetic nervous system activity [36,62,63]. However, training intensity may be implemental in cardiac sympathetic adaptation. Plourde *et al.* have reported that exercise-trained rats demonstrate reduced ventricular β -adrenergic receptor quantities and, more specifically, those existing in the high-affinity state and have proposed that training induced a reduction in the coupling between the β -adrenergic receptor and signal transduction through G proteins [62]. Heller *et al.* have suggested impairment of myocardial reactivity to selective β_1 -adrenergic stimulation in diabetic rats expressed as significant depressions in heart rate and contractility to dobutamine [64]. Exercise-mediated increase in sympathetic activity heightened myocardial responsiveness to adrenergic stimulation by down-regulation of receptors [64]. However, the

literature addressing training-induced adrenergic modification is conflicting as no apparent differential in the number of β -adrenergic receptors in ventricular tissue from diabetic rats, trained or sedentary despite improvement in the diabetic state of trained rats [3,46,63]. However, Sylvestre-Gervais *et al.* have reported a training-induced reduction of both the total number and density of β -adrenoceptors in heart ventricular tissue with no apparent alterations in their affinity constant, potentially attributable to an increase of basal epinephrine secretion [3,46,63]. Alternatively, STZ-induced hypothyroidism is a suggested potentiality in the down-regulation of cardiac β -adrenoceptors as thyroidectomised rats seemingly withstand receptor diminishment [36]. The inception of STZ β -adrenoceptor decline has been inconsistently reported, however a gradually occurring receptor adaptation has been suspected. The incompatibility of available evidence on adrenergic receptor modulation may relate to differences in experimental protocols and training induction, β agonists employed, and severity of the diabetic state [64].

9. AUTONOMIC ACCOMMODATIONS TO EXERCISE TRAINING

Typically for the healthy individual, increased heart rate occurring under light physical activity is due to withdrawal of vagal efferent tone [16]. Conversely, maximal heart rate occurring under higher work loads has been attributed to sympathetic dominance of sinoatrial node function [16]. Negrao *et al.* have detailed the sympathetic and parasympathetic autonomic contributions to heart rate regulation in exercise-trained rats. Heart rate accordingly increased with exercise intensity and was attributable to withdrawal of vagal tone. In exercise-trained rats, on the other hand, the vagal effect persisted compared to sedentary counterparts where the sympathetic stimulation of the sinus node increasingly dominated and tachycardia more rapidly ensued [65]. The effects of exercise training on autonomic and hemodynamic dysfunction, particularly arterial pressure, heart rate and autonomic control in STZ-diabetic rats have been evaluated by De Angelis *et al.* [66]. Induction of hypotension, autonomic dysfunction and depressed myocardial function in sedentary diabetic rats have been associated with diminished heart rate response to increasing sub-maximal exercise intensities [27,36,66]. Additionally, altered cardiac baroreceptor sensitivities have been documented in diabetic rats [36]. Howarth *et al.* have observed that the rapid decline in physical activity levels in STZ-rats may be attributed to a reduction in heart rate, body temperature and heart rate variability. Furthermore, an altered sympathovagal modulation of heart rate or interrupted sinoatrial node function may be responsible for these observations [4]. De Angelis *et al.* have observed an increase in resting heart rate in trained diabetic rats that was associated with alterations in intrinsic heart rate as a potential function of improved sinoatrial pacemaker regulation and subsequent reduction in vagal tonus [66]. Mokhtar *et al.* have suggested that high-energy phosphate availability is limited in the diabetic rat heart and therefore may be partly accountable for the observed depression in cardiac function and heart rate described in these animals [48]. Proposed enzymatic mechanisms for the diminution of heart PC levels have included impairment of mitochondrial oxidative phos-

phorylation and intracellular energy transport by means of creatine kinase isozyme disequilibrium and accumulation of long-chain acyl-CoA esters within the myocardium [47,48]. Training-induced improvement in the sinoatrial node function in diabetic rats has been attributable to the reduction of long-chain acyl-CoA levels occurring secondary to improved myocardial lipid metabolism as well as enhanced ATP levels in the hearts of diabetic rats [47].

Dual limbs of the autonomic nervous system, namely parasympathetic and sympathetic modalities, reciprocally contribute to the regulation of heart rate during physical exertion [16]. Exercise-mediated alterations in the function of the parasympathetic nervous system as it relates to cardiovascular control have been investigated. The induction of exercise-induced resting bradycardia in healthy subjects has been well documented [16]. However, a pathological decrease in resting heart rate in STZ-diabetic rats was not attributable to training-induced bradycardia. Furthermore, no evident cholinergic adaptations to endurance exercise training despite marked improvement in aerobic capacity occur within the autonomic nervous system of diabetic rats. Speculatively, improvements in cardiac functional capacity in trained diabetic rats has been attributed to contracting muscular adaptations or sympathetic input to the heart, influential in both rate and contractility [27].

10. CONCLUSIONS

Routine physical activity has been observably related to improved weight management, lipid profile, endothelial function, inflammatory defense systems, insulin sensitivity, glucose homeostasis, and cardiac performance in humans and rats models of diabetes mellitus [6-9,67]. Precise definition of the physiological outgrowths of aerobic exercise training in the experimental diabetic rat model may unveil the enigma of insulin resistance or deficiency in the myocardium and skeletal muscle of human diabetic and insulin resistant patients. Furthermore, study of the alterations in the STZ-diabetic rat myocardium is indispensable in unveiling the early physiological progression of diabetic cardiomyopathy as human patients may not be suitably studied in this capacity [36]. As formally ascertained, at a given level of genetic susceptibility, carbohydrate and lipid disequilibrium, physical inactivity and substandard cardiorespiratory fitness are indispensable antecedents to the evolution of diabetes mellitus [13]. Furthermore, critical analysis of the evidences presented herein may facilitate in assessing the risks and benefits of physical activity for the diabetic patient, particularly as a sedentary lifestyle is considered a modifiable risk factor in diabetes development and cardiovascular sequelae [67]. Arguably, the homeostatic responses to physical training are seemingly dependent on the type and severity of diabetes and the intensity, duration, frequency, and timing (prior to disease onset or preceding disease development) of aerobic exercise in both humans and experimental diabetes.

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