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The FITT Principle in Individuals with Type 2 Diabetes: From Cellular Adaptations to Individualized Exercise Prescription

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Author's contribution

The sole author designed, analyzed and interpreted and prepared the manuscript.

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ABSTRACT

Diabetes mellitus is a complex disease that affects millions of people worldwide. Type 2 diabetes (T2DM) arises from a combination of genetic susceptibility and environmental factors, including physical inactivity and poor nutritional habits. Accumulating evidence suggests that the majority of T2DM cases can be prevented through diet, physical activity, and exercise modification. Acute exercise bouts improve glucose homeostasis by increasing skeletal muscle glucose uptake through insulin-dependent and non-insulin dependent pathways; whereas, chronic exercise training induces alterations in genes' expression, promoting mitochondrial biogenesis, glucose transporters (GLUT4) expression and protein enhancements, and fiber type transformation. However, individuals with T2DM show a low participation and poor adherence to exercise training. Alterations in metabolic, vascular and neural function induced by T2DM may impede skeletal muscle blood-flow during exercise, contributing to exercise intolerance. Thus, appropriate exercise programs that will improve glycemic control and will be attractive and effective for the individual with diabetes are still needed. The purpose of this article is (i) to present cellular mechanisms through which exercise can improve glycemic control, (ii) to describe the exercise prescription characteristics (frequency, intensity, time, type; FITT) required to achieve optimal benefits in T2DM, and (iii) to

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highlight the pathophysiological alterations induced by T2DM and obesity that should be considered when designing an exercise program. Genetic predisposition, diabetes/obesity phenotypes, oxidative stress, brain insulin sensitivity, perceived exertion, and initial fitness levels or training experience influence the inter-individual variability in exercise responsiveness. Thus, exercise is prescription should be individualized in order to achieve maximal benefits and high adherence.

Keywords: Diabetes; exercise; glycemic control; cardiovascular; insulin resistance; glucose transport; muscle oxygenation.

1. INTRODUCTION

Type 2 diabetes (T2DM) is a complex disease that affects millions of people worldwide [1]. T2DM leads to microvascular (neuropathy, nephropathy, retinopathy) and macrovascular (ischemic heart disease and peripheral vasculopathy) complications that contribute to high morbidity and mortality rates [2,3]. Its prevalence is continuously increasing; it is expected that, by the year 2040, 642 million people will suffer from T2DM (1 out of 10 adults), the latter being the seventh leading cause of death [1,2,4]. Accumulating evidence however, strongly suggests that the majority of T2DM cases can be prevented through diet and lifestyle (i.e. physical activity and exercise) modification [5-7]. However, individuals with diabetes and cardiovascular disease have a low participation and a poor adherence to exercise training programs [8-10]. Thus, appropriate individualized exercise programs that will improve the glycemic control and cardiovascular status and will be attractive, reducing the drop-out rates, are still needed. The purpose of this article is (i) to present the cellular mechanisms through which exercise can improve glycemic control in T2DM, (ii) to describe the characteristics of exercise prescription (frequency, intensity, time, and type; FITT) required to achieve optimal benefits, and (iii) to highlight the pathophysiological alterations induced by T2DM that should be taken into consideration when designing the exercise program. Factors influencing the inter-individual variability in the responsiveness to exercise and alterations impeding muscle oxygenation and inducing exercise intolerance will be discussed.

2. THE ROLE OF OBESITY IN THE PATHOGENESIS OF T2DM

T2DM is characterized by sustained elevations in plasma glucose associated with main defects in insulin resistance (or reduced responsiveness to insulin) and abnormal insulin secretion by pancreatic islet β-cells [11]. T2DM arises from a combination of genetic susceptibility and environmental factors, such as physical inactivity and excessive caloric intake, exposure to chemical or viral substances (smoking, adenovirus 36), emotional stress and depression [4]. Poor nutritional habits, in particular diets with high dietary glycemic load and trans fatty acids, have also been associated with an increased risk for diabetes [4,5]. Obesity has been considered a driving force for T2DM in the majority of cases [6]. As body weight and body fat increase, insulin resistant increases, leading to impaired glucose tolerance, and an increased risk of developing T2DM. In fact, adipocyte cell size has been shown as an independent predictor of insulin resistance and risk for T2DM [12,13]. More specifically, the adipose cell enlargement in obesity leads to a pro-inflammatory state, resulting in turn, in increased secretion of cytokines, such as interleukin-6 or -8, MCP-1, and TNF-α, and reduced secretion of adiponectin [14,15]. The increased inflammatory cytokine secretion contributes to recruitment of macrophages into the adipose tissue and impairs pre-adipocytes differentiation. These alterations promote local insulin resistance and thus, an impaired inhibitory effect of insulin on fatty acid release, while encouraging ectopic lipid storage in non-adipose tissues, such as the liver and the skeletal muscle [14-16].

Fatty acids that cannot be stored in adipose tissue, enter the systemic circulation, resulting in an oversupply of systemic fatty acids that need to be oxidized by the skeletal muscle cells. However, in obesity and T2DM, there is a 30% decrease in size and number of mitochondria and dysfunctional mitochondrial proteins within the skeletal myocyte [17-22]. Thus, fatty acid oxidation might not be nearly sufficient to meet the very high rates of their uptake [23-26]. The mismatch of fatty acid uptake to oxidation, can result in an accumulation of fatty acid intermediates, such as ceramides, diacylglycerides, and long-chain fatty acyl-CoA, within the skeletal myocyte and increased

oxidative stress, which have been suggested to impair insulin signaling and to induce insulin resistance [27,28]. All of these events could lead to a vicious cycle in which mitochondrial dysfunction, elevation of systemic fatty acids, impaired lipid oxidation and insulin resistance amplify each other [29]. Yet, whether mitochondrial dysfunction is primary (i.e. the critical initiating defect) or secondary to the subtle derangements in glucose metabolism, insulin resistance, defective insulin secretion and inactivity in the pathogenesis of T2DM is a topic of debate [11]. Despite many studies on this issue, there is still a controversy whether perturbations in mitochondrial functional capacity are a cause, a consequence, or a contributor to insulin resistance and T2DM [11,21,30,31].

3. THE ROLE OF EXERCISE IN THE IMPROVEMENT OF MUSCLE GLUCOSE UPTAKE AND INSULIN RESISTANCE

Exercise has been considered a cornerstone treatment for diabetes and obesity-related metabolic complications. Systematic exercise training in individuals with insulin resistance/ T2DM initiates transcriptional and translational mechanisms that (i) promote angiogenesis (by inducing an upregulation of angiogenic factors, such as VEGF and miRNA-126) and (ii) increase skeletal muscle oxidative capacity (by increasing the number of mitochondria and by improving respiratory chain and other oxidative enzymes' function) [32-40]. Involvement in regular exercise sessions could lead to increased fatty acid oxidation, reduced accumulation of fatty acid intermediates, less inactivation of the insulin receptor, and better insulin signaling [41].

Even a single exercise session can improve glycemic control by exerting acute changes at the extracellular, at the membrane and within the skeletal muscle cell. More specifically, during exercise, skeletal muscle blood flow increases dramatically. There is capillary recruitment, in order to increase the available surface area for exchange of oxygen and other respiratory gases, and promote delivery of nutrients, such as glucose and fatty acids. This capillary recruitment is achieved by the synergetic action of the sympathetic nervous system and secretion of hormones, such as insulin [42,43]. Insulin increases microvascular perfusion by causing vasodilation in terminal arterioles that control access to nutritive capillary beds of the muscle that are receiving little, intermittent, or no blood flow in the basal state [43,44]. Even though during acute exercise, plasma insulin concentrations decline, the increase in blood pressure and muscle blood flow ensures insulin delivery. Consequently, insulin-stimulated microvascular perfusion increases, securing improved glucose delivery [45]. At the membrane level and within the skeletal myocyte, exercise induces alterations in the number and activity of transporters, stimulating glucose uptake. Indeed, insulin and exercise stimulate glucose uptake through two distinct signaling mechanisms: an insulin-dependent pathway and a non-insulin dependent pathway.

The insulin-dependent pathway of glucose uptake begins with insulin binding to its receptor, inducing rapid site-specific tyrosine phosphorylation of the insulin receptor and phosphorylation of the insulin receptor substrate-1 (IRS-1). Through the activation of phosphatidylinositol 3-kinase (PI3K) pathway and the Ser/Thr protein kinase Akt phosphorylation through the Akt substrate of 160 kDa, AS160, insulin-stimulated glucose transport is initiated [16]. These actions lead to the translocation of glucose transporters (GLUT4) from an intracellular location (mainly in the trans-Golgi network region and within small tubulovesicular structures) to the cell membrane, facilitating glucose uptake into the cell [46,47].

The non-insulin dependent pathway is stimulated during exercise, inducing GLUT4 translocation and promoting further glucose uptake [48-50]. In more details, reports in knockout mice that lack insulin receptors in skeletal muscle showed that these animals maintained an exercise-stimulated glucose uptake [49]. Similarly, humans with impaired glucose tolerance had impaired insulin-stimulated but not exercise-stimulated glucose uptake [51]. Different studies were conducted to elucidate the exact pathway of this exercise-stimulated glucose uptake. Using caffeine to induce Ca^{2+} release from the sarcoplasmic reticulum (through opening of the ryanodine receptors), it was demonstrated that an increase in intracellular Ca^{2+} through the activation of AMP-activated Protein Kinase (AMPK), induces GLUT4 translocation and increases muscle glucose uptake, without necessarily requiring membrane depolarization [39,40,52]. Further experimental evidence showed that the although depolarization induced Ca^{2+} release from the sarcoplasmic reticulum does not seem to regulate glucose transport directly, Ca^{2+} dependent signaling and other Ca^{2+} sources

contribute to the regulation of glucose during contraction. More specifically, Ca^{2+} binding to calmodulin and activates the CaMKII complex inducing hyperacetylation of histones in the vicinity of the myocyte enhancer factor 2 (MEF2) domain and increases MEF2 binding to its cis element, influencing MEF2-dependent Glut4 gene expression [39,40,53,54]. In turn, this allows an increase in transcriptional factors and RNA polymerases, and increased GLUT4 protein levels [39]. AMPK and its primary upstream kinase, LKB1, are proteins involved in glucose transport during muscle contraction. During exercise, the increase in the AMP/ATP ratio stimulates AMPK leading in an increase in muscle glucose uptake [55-57]. An involvement of calcineurin, a Ca^{2+}/calmodulin-dependent protein phosphatase, and p38-mitogen activated protein kinase (p38-MAPK) have also been proposed by some but not all studies [58-60]. Although there is evidence for a potential role of nitric oxide synthase (NOs) in the control of contraction-induced glucose uptake, this effect seems to be fiber type dependent (limited to fast-twitch muscle); the exact pathway is still under investigation [52,61-65].

Within the muscle cell, glucose phosphorylation by hexokinase II (HKII) is another important step influencing GLUT4 translocation [66]. Although, at resting conditions, HKII overexpression in transgenic mice did not result in an increase in muscle glucose uptake, during exercise, HKII overexpression did stimulate glucose uptake [67]. On the other hand, GLUT4 overexpression, in the absence of HKII overexpression, had little effect on muscle glucose uptake during exercise [67]. These studies in mice suggest that the ability to phosphorylate the transported glucose in the muscle cell is a rate-limiting step in glucose utilization during exercise [66,68].

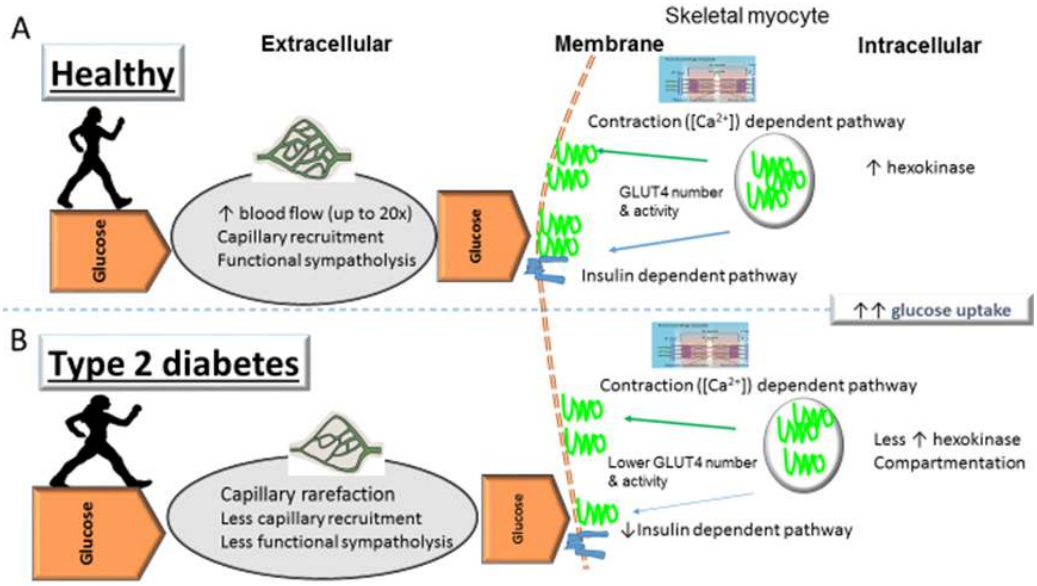

Fig. 1. A. In healthy normoglycemic individuals, exercise improves glycemic control by inducing alterations at the extracellular space, at the membrane and inside the skeletal myocyte. More specifically, during exercise there is functional sympatholysis and capillary recruitment. As a consequence, blood flow to the active skeletal muscle increases, promoting glucose delivery to the skeletal muscle. At the skeletal myocyte level, exercise increases glucose uptake by activation of insulin-dependent (through activation of phosphatidylinositol 3-kinase) and contraction-induced (associated with the rise in cytosolic Ca^{2+}, activation of AMP protein kinase, and Ca^{2+}/calmodulin complex) pathways. The increase in hexokinase during exercise also stimulates glucose uptake. B. In individuals with type 2 diabetes, capillary rarefaction, endothelial dysfunction, and reduced functional sympatholysis can impede blood flow and glucose or oxygen delivery to the muscle. Although the insulin-dependent pathway is dysfunctional in these individuals, the contraction-dependent pathway is intact and can be used to increase blood glucose uptake by the skeletal muscle and lower blood glucose concentrations

The above studies demonstrate that (i) insulin and exercise mediate GLUT4 translocation in skeletal muscle through distinct proximal signaling mechanisms and (ii) muscle contraction activates multiple signaling pathways that possibly act synergistically to promote an increase in glucose uptake. The insulin-dependent pathway appears dysfunctional in individuals with T2DM, in several steps within the insulin cascade, namely reduced IRS, PI3K and Akt response to insulin-stimulus. However, the non-insulin dependent pathway is intact and can be used to lower blood glucose concentrations [69-71]. Summarizing, an acute bout of exercise improves glucose homeostasis by increasing skeletal muscle glucose uptake, whereas chronic exercise training induces alterations in genes' expression promoting mitochondrial biogenesis, increases GLUT4 expression/protein and encourages fiber type transformation, possibly through a peroxisome-proliferator-activated receptor-γ-coactivator 1α (PGC-1α) dependent pathway [33,40] [72]. The acute increases in cytosolic Ca^{2+} related signaling proteins including CaMKII, AMPK and MEF2, p38 MAPK, and calcineurin during muscle contractions (induced by mechanical and metabolic stress) lead to increases in PGC-1α expression and chronic adaptations [72,73]. The extent of the chronic adaptations are dependent upon the characteristics of the exercise program (FITT principle) [74].

4. CHARACTERISTICS OF THE EXERCISE PROGRAM

The FITT principle refers to the (F)requency, (I)ntensity, (T)ype and (T)ime of the prescribed exercise program.

4.1 Frequency

In both rat and human skeletal muscle, GLUT4 mRNA concentrations were 2- to 2.5-fold higher within 3 h after an acute single bout of exercise, associated in an increase in GLUT4 protein content by 1.5 to 2-fold within 16 -24 h after an exercise bout [75]. Although GLUT4 protein content has been shown to increase with consecutive daily bouts of exercise, a steady-state level is reached within a few days. GLUT4 concentrations are 2- to 3-fold higher in individuals following systematic training than sedentary controls; however, the effects of exercise on glucose uptake are short-lived (up to 24 hours) [76-78]. The above reports emphasize the importance of the frequency of exercise training, in order to maintain the exercise-induced benefits on GLUT4. After 4 - 6 days without exercise, insulin sensitivity has been shown to return to untrained levels, as inactivity induces gene expression associated with insulin resistance and DNA methylation of PGC-1α [77-79]. For this reason, it seems plausible to recommend that exercise should be performed systematically on most days of the week, with no more than 2 days to elapse between activity sessions to maintain higher levels of insulin sensitivity [80].

4.2 Intensity and Type

Endurance training, generally defined as exercise involving several large muscle groups that aims to improve cardiorespiratory fitness, includes activities such as fast walking, running, biking or swimming. In T2DM, performing endurance exercise is important because (i) during this type of exercise, oxidative fibers (i.e. fibers expressing myocin heavy chain I; type I) are recruited, (ii) type I fibers present a 20% higher GLUT4 content than type II fibers, and (iii) patients with T2DM have lower type I fibers compared with normoglycemic controls [81,82]. It has been recently shown that not only human type I fibers have a greater abundance of GLUT4 proteins (by 29%) compared with type IIx fibers, but they also exhibit greater HKII (by 470%) and electron transport chain complex II (by 35%); thus the ability to transport, phosphorylate, and oxidize glucose, respectively, in type I fibers is greater [83]. Type I fibers also have higher glycogen synthase levels (by 35%) vs. type II; hence, their ability to synthesize muscle glycogen and contribute to the reductions of blood glucose concentrations is greater. In individuals with T2DM lower insulin receptor content, insulin-stimulated glucose disposal rate, glucose oxidation rates and non-oxidative glucose metabolism have been demonstrated compared with lean and obese individuals [83]. Yet, most differences in insulin phosphorylation among groups in the aforementioned study, were due to the different protein levels between fiber types [83]. The fewer type I fibers and the higher number of type IIx fibers in muscles from patients with T2DM seem to play the major role to the reduced glucose disposal rate under insulin-stimulated conditions compared with lean and obese subjects without T2DM. After two weeks of low intensity exercise training, an 25% increase in GLUT4 protein content in type I fibers obtained from the vastus lateralis muscle was observed in young healthy men, but not in type IIa or type IIx

fibers [82]. These findings suggest that GLUT4 protein levels are related to the fiber type mainly recruited during the training sessions [82]. Furthermore, experiments in T2DM rats showed that low intensity running is beneficial in improving the capillary volume and mitochondrial markers, and pro-angiogenic factors concentrations, such as VEGF [37]. In elderly, even a low-intensity exercise program for 6 weeks (comprised of low intensity and low-volume resistance exercises), which would ordinarily be insufficient for improving aerobic fitness or lipidemic profile, was found to be effective in improving insulin resistance, independently of improvements in body weight [84].

Studies examining the relationship between exercise intensity and the improvement in insulin sensitivity reported partly contradictory results [85]. While some studies reported better effects of high intensity exercise (75 - 80% of VO_2peak) on insulin sensitivity, other studies did not find differences in GLUT4 concentrations and/or insulin sensitivity between moderate and high intensity training [86-90]. In mice and in humans, endurance exercise of higher intensity enhanced hexokinase concentration/activity and promoted greater glucose uptake [66,91]. More specifically, in humans, speed endurance training acutely increased HKII mRNA more than lower intensity endurance exercise, providing a stimulus for muscle mitochondrial biogenesis, substrate regulation, and angiogenesis [91]. While improvements in insulin sensitivity were more related to exercise intensity, reductions in glycosylated hemoglobin (HbA_{1c}) seem to be more strongly linked to the training volume [92]. In support, a recent systematic review suggested that exercise at higher intensity for those who can tolerate it, seemed to offer superior fitness benefits, while longer duration programs optimized reductions in HbA_{1C}.

In recent years, the effects of high intensity interval training (HIIT) on glycemic control in healthy and diabetic individuals has gained interest. HITT is a form of exercise where individuals perform successive exercise bouts of relatively short duration (usually from 30 s to 2 min) at high intensity workloads (≥90% VO_{2peak}), alternated with equal periods of active (30% of VO_{2peak}) or passive rest. This type of exercise promotes a high degree of muscle fiber recruitment, activation of AMPK, and depletion of glycogen, while it increases GLUT4 and mitochondria content in younger and older adults [38,93-96]. HITT promotes fast metabolic adaptations; therefore, it has been emerged as an alternative to continuous moderate intensity exercise. In patients with T2DM, six sessions of HIIT training (10×1 min cycling bouts at 90% maximal heart rate with 1 min rest in between) over 2 weeks significantly improved glucose regulation (GLUT-4 transporter abundance) and skeletal muscle mitochondrial content [96]. In diabetic mice, apart from the greater increase in GLUT4 and higher insulin-stimulated Akt phosphorylation, HITT improved glucose uptake more efficiently than moderate continuous training by mechanisms independent of mitochondrial adaptations [97]; further studies in humans are needed. HITT also induced greater improvements in micro- and macro-vascular reactivity than continuous exercise in patients with T2DM [98]. However, it should be noticed that only in a few studies examining the acute or chronic effects of exercise intensity on the improvements of glycemic control, between the different exercise sessions (low, moderate, and high intensity) or modes of exercise (resistance vs. aerobic, continuous vs. HITT), the total work performed or the overall physiological stress was matched [99,100]. Zafeiridis et al. using NMR-based metabonomics showed that acute continuous and interval exercise sessions, when performed with similar effort and physiological strain (i.e. same overall physiological stress), induce comparable global metabolic responses despite their marked differences in work-bout intensities (80% vs. 95 - 110% of VO_{2max}, for continuous and interval, respectively) [101]. Kraniou et al. also showed that moderate and high intensity exercise (40 and 80% of VO_{2peak}, respectively) when performed with equal total work (by altering the duration of the exercise session at 60 min and 27 min, respectively), result in increases in GLUT4 mRNA and protein to a similar extent [102]. The effects on postprandial hyperglycemia were also not different between a HIIT and a continuous moderate intensity exercise (30 min at approximately 65% of heart rate peak) session of equal work in overweight or obese adults [103]. Yet, HITT seemed to have longer lasting effects as postprandial glycaemia on the following day was lower following HIIT than continuous exercise. Although the acute effects of exercise on glycemic control are mirrored in the chronic adaptations induced by training [94], larger randomized controlled trials of longer duration are required to confirm whether exercising at higher intensities is well-tolerated by patients with T2DM without increasing drop-out rates.

4.3 Time (Duration)

Structured exercise programs with durations of > 150 min per week were associated with greater HbA_{1c} declines (by 0.89%) and improvements in insulin sensitivity than those with durations of < 150 min (reductions in HbA_{1C} by 0.36%) regardless of exercise intensity [104,105]. Total exercise duration should thus be considered when designing training programs with the intent of improving insulin action. In current guidelines, adults with T2DM, are also encouraged to interrupt prolonged periods of sitting with 15 min walking (especially after meals) and either light walking or muscle strengthening activities undertaken for 3 min after every 30 min of inactivity in order to improve overall glycemic control [80].

5. THE CURRENT FITT GUIDELINES IN T2DM

Current guidelines for FITT by the American Diabetes Association state that individuals with T2DM should engage in aerobic exercise most days of the week, performed at least at moderate intensity (i.e. > 40 - 60% of heart rate reserve or VO_2 reserve, which corresponds at 55-76% of maximal heart rate or ''12-13'' on the Borg's scale, i.e. somewhat-hard) at a minimum of 150 min/week [80]. Individuals with T2DM should also engage in muscle strengthening exercise of 1 - 3 sets of moderate to vigorous intensity [70-75% of a repetition maximum (1RM) or 10 - 12 repetitions to fatigue] of 6-8 different exercises involving large muscle groups [80,106]. Strength training for 30 min, three times per week increases insulin action (by increasing content of GLUT4 protein, insulin receptor and glycogen synthase) [107]. High-intensity, multiple sets may emerge as the prescription of choice for individuals with impaired fasting glucose without other cardiovascular complications [106]. Muscle endurance exercises (i.e. increasing repetitions to 20 while decreasing the load and the rest interval between sets) offers a useful alternative for patients unable to perform the higher intensity of resistance training (due to musculoskeletal pain or other co-morbidities). Lower-body and core strengthening exercises can also improve balance. In a systematic review [105], structured aerobic exercise was associated with a greater decline in HbA_{1c}, than structured resistance training. In contrast, another study reported that resistance exercise was superior to aerobic or no exercise for improving overall physical health status, as assessed by the Well-Being Questionnaire [108]. While many reports showed statistically significant differences in various measurements of glycemic control between the two exercise modes, there was no evidence of these differences having clinical importance or different impact on cardiovascular risk markers or safety [109,110].

Combining aerobic with resistance exercise resulted in greater improvements in insulin sensitivity than aerobic or resistance exercise alone [111,112]. Here again, it should be noticed that in many studies the volume of exercise among the different exercise modes was not matched (i.e. the combined exercise group trained for twice as much time as either mode of exercise alone). More studies are needed to determine whether greater improvements with combined exercise are due to synergistic effects of the two very different exercise modes, or whether the effects were due to a greater amount of exercise, or a combination of both [113]. Nevertheless, as T2DM is associated with multiple neuromuscular defects and reduced muscle strength, resistance exercise should be an essential part of the exercise program [114]. In fact, low muscle mass was associated with an increased risk of T2DM, independent of general obesity, in middle-aged and older adults [115].

6. INTER-INDIVIDUAL VARIABILITY IN THE EXERCISE-TRAINING RESPONSIVENESS

An important issue when designing an exercise program is the large inter-individual variability in the exercise-training responsiveness [116,117]. Some individuals responding strongly to exercise ("high-responders"), while some others to a very limited extent ("low-responders") [117]. High-responders seem to activate key genes to a greater extent than low-responders. Genetic variability, differences in brain insulin sensitivity, oxidative stress, as well as diabetes and obesity phenotypes seem to partly explain training responsiveness [117-121]. High-risk diabetes phenotypes were associated with low improvements in glycaemia during a lifestyle intervention [120]; however, further studies are needed to clarify the mechanisms for the variability in exercise responders and non-responders.

Another important concern in exercise prescription in patients with diabetes is their intolerance to exercise and their high drop-out rates [8,9]. All the above, highlight the

importance of designing individualized exercise programs, aiming at optimizing glycemic control and improving fitness in the patient with T2DM, while ensuring adherence to exercise. In the next section, factors that should be taken into consideration when prescribing an individualized exercise program to the diabetic population are presented.

7. PHYSIOLOGICAL FACTORS TO CONSIDER WHEN DESIGNING AN INDIVIDUALIZED EXERCISE TRAINING PROGRAM FOR T2DM

Designing an exercise program for an individual with T2DM, even without the presence of complications, is more challenging than in a normoglycemic individual. Chronic hyperglycemia can alter the acute and chronic adaptations to exercise. Although ample scientific evidence suggests that the greater the volume of exercise the greater the benefits in muscle glucose uptake, the individual with T2DM might not be able to tolerate the prescribed exercise. Capillary rarefaction, reduced microvascular reactivity, functional sympatholysis, and over-activity of the exercise pressor reflex could impede oxygen and nutrients' delivery during exercise and contribute to an exaggerated blood pressure response during exercise and/or to exercise intolerance [122-124]. More specifically, during exercise, there is capillary recruitment in order to increase the available surface area for exchange of oxygen and respiratory gases, and promote delivery of nutrients, such as glucose and fatty acids. However, insulin resistance can impair the insulin-mediated microvascular responses in skeletal muscle, possibly limiting capillary recruitment, as it has been shown in rats [125]. In addition, during exercise, an optimal regulation of vascular tone by endothelial cells is required. That is, endothelial cells should have an adequate capacity to respond to mechanical and chemical stimuli, to form a sufficient amount of vasoactive substances, and induce local vasodilation in the active skeletal muscle in order to facilitate perfusion. However, in individuals with T2DM there is capillary rarefaction (less functional capillaries or reduced capillary density) and endothelial dysfunction (alterations in endothelial cells phenotype and functional characteristics) [126-128]. The reduced lumen diameter and thickened smooth muscle cell layer, along with alterations in sympathetic control, result not only to a reduced ability to maintain proper vascular tone at resting conditions, but also to a reduced vasodilatory capacity during exercise. In humans, even in a pre-diabetic state, skin microvascular reactivity was blunted [129]. Studies in diabetic rats showed that 8 weeks of moderate hyperglycaemia was sufficient to induce morphological changes, i.e. vascular remodelling in mesenteric arteries, whereas, severe hyperglycemia caused endothelial dysfunction [126,129]. Moreover, in animals and humans with diabetes, a reduced NO availability and a blunted vasodilatory responsiveness to an NO donor was reported, suggesting that smooth muscle cells are less sensitive to the NO stimuli [130-133]. The vasodilatatory effect of the purinergic system, such as adenosine, was also severely reduced in patients with T2DM [134]. These alterations could contribute to reduced functional sympatholysis (i.e. less vasodilation in the exercising muscle) and limit the amount of blood and oxygen supplied to the exercising muscle. In fact, during submaximal exercise, femoral blood flow and leg vascular conductance was attenuated in individuals with T2DM compared with healthy adults [28,135]. Even a mild and relatively transient period of insulin resistance, as observed in gestational diabetes mellitus (GDM), was associated with blunted microvascular reactivity within the skeletal muscle, accompanied by reduced muscle oxygenation during intermittent handgrip exercise [124] compared with uncomplicated pregnancies. The dysfunctions in muscle oxygenation during exercise in treated women with GDM were correlated with macrovascular stiffness and cardiovascular risk factors, independently of BMI. Although women with GDM had similar maximal handgrip strength to their control counterparts, the former group exhibited signs of exercise intolerance during repeated contractions [124].

Obesity can also contribute to hyperglycemia-induced impairments in functional sympatholysis, setting up a vicious cycle that causes a progressively greater decrease in blood flow to the exercising muscle. Alterations in baroreceptor sensitivity, an enhanced exercise pressor reflex (consisting of two components, the mechanoreflex and the metaboreflex), and/or arterial stiffness can cause an exaggerated exercise blood pressure response in individuals with obesity and/or metabolic syndrome [136-140]. Using involuntary exercise (contractions induced by whole body-vibration platform), we have previously shown that even normotensive women with obesity can exert an exaggerated blood pressure response, suggestive of an

overactive mechanoreflex in these individuals [141]. In contrast, the metaboreflex in obese individuals has been reported to be blunted [142]. Alterations in these reflexes result in an imbalance of the sympathetic / parasympathetic outflow and may cause a blunted heart rate response at higher exercise intensity in obesity and delayed recovery [143-146]. All of these factors can modify the cardiovascular responses during exercise in an individual with T2DM and obesity. Furthermore, alterations in central command, a reflex originating from higher brain regions, can influence the acute responses to exercise, exercise perception and tolerance. Recent reports showed that reduced brain insulin sensitivity, associated with visceral obesity and diabetes, can cause alterations in the hypothalamic/prefrontal cortex, in the hippocampus, and in certain higher cortical brain regions [147]. These changes could affect motor control and perception. In addition, at higher exercise intensities cerebral oxygenation and blood flow started to decrease in obese, whereas it plateaued or increased in lean individuals [148]. These factors can contribute to the reduced exercise tolerance of the individual with diabetes. The exact mechanism, however, is still under investigation and further studies that will examine whether exercise training can increase cerebral oxygenation and modify exercise tolerance, are needed.

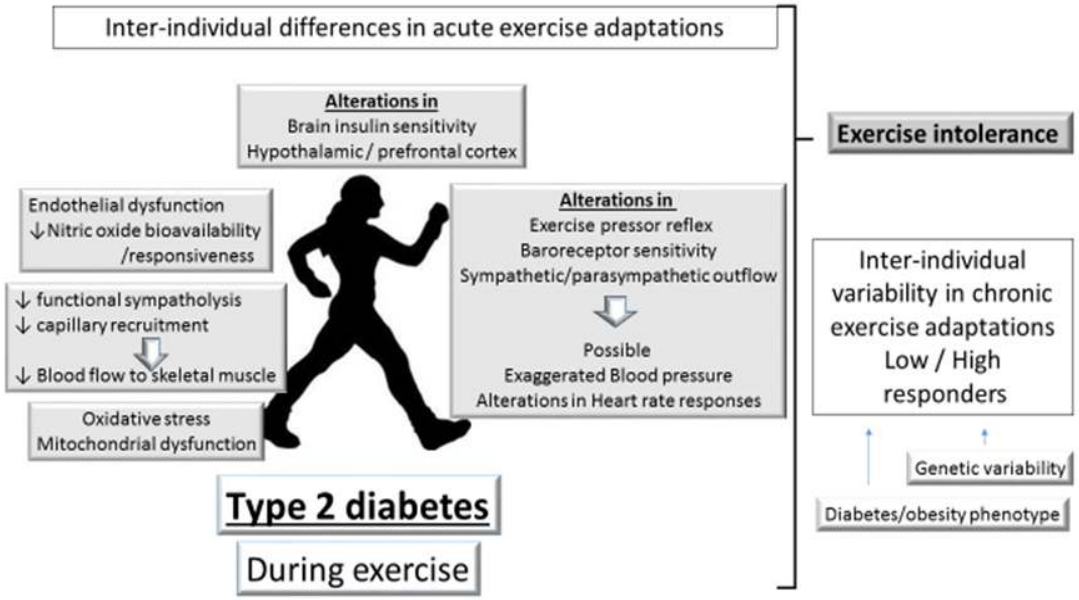

Fig. 2. A. Inter-individual differences in physiological factors should be considered when designing an exercise training program in individuals with type 2 diabetes: (i) capillary rarefaction and lower capillary recruitment result in reduced glucose, oxygen, and nutrients delivery in the exercising individual with diabetes, (ii) the lower mitochondrial number and dysfunctions in the respiratory chain lead to a poor functional capacity (reduced ability to maintain work), (iii) an overactive exercise pressor reflex, along with blunted baroreceptor sensitivity, could alter sympathetic/parasympathetic outflow, contributing to an exaggerated blood pressure response and alterations in the heart rate responses during exercise and recovery, and (iv) alterations in cerebral hypothalamic and prefrontal cortex (areas responsible for motor control) can induce premature fatigue and exercise intolerance. Thus, these individuals might not be able to tolerate moderate-high intensity exercise, at least at initial stages. Frequent, low-intensity activities might be preferred for those individuals. B. Genetic predisposition along with different diabetes/obesity phenotypes, oxidative stress, and initial fitness levels could influence the training responsiveness and degree of adaptations. In low responders, a longer time before readjusting the exercise volume or choosing a different exercise modality might be necessary

The above functional alterations suggest that in individuals with T2DM and obesity (i) blood pressure should be monitored even in normotensive participants, at least in the initial stages of exercise training, (ii) fatigue might appear earlier than in healthy individuals, when exercising at a similar relative intensity of exercise, and (ii) the rate of perceived exertion is then a good index for evaluating exercise intensity, especially if autonomic dysfunction exists. Even though higher intensity exercise results in great improvements in glucose utilization, it also results in a high perceived exertion [96]. Thus, at initial stages of the exercise training, frequent, low-intensity activities may be a better choice [149]. In inactive individuals with low insulin sensitivity, even an exercise dose of 400 kcal/week (about 40% of the proposed by current guidelines) was associated with a significant improvements in insulin sensitivity and autonomic dysfunction [85, 149]. It should be noticed, however, that it may take a longer time (> 12 weeks) to observe improvements after low-volume training [150]. As exercise training progresses, in combination with the augmented muscle glucose uptake and mitochondrial biogenesis, capillarization and capillary recruitment increases, brain insulin sensitivity and the exercise pressor reflex improve [122,151]. When improvements in hemodynamic/neurohormonal responses occur, then programs of higher intensity could be better tolerated. A further increase in exercise volume is then required to promote additional improvements in insulin sensitivity [74,104,106]. Future research should be conducted to directly compare whether (i) individualized programmes with low intensity, frequent exercise sessions result in a better adherence to exercise training and better long term glycemic control in individuals with T2DM than high intensity raining or conventional moderate intensity training.

8. CONCLUSION

In conclusion, phenotypic variability in T2DM and obesity do exist, suggesting that exercise prescription should be individualized. The patient's physical activity status, previous exercise experience, body composition and degree of obesity, perceived exertion, autonomic function and blood pressure response to exercise should be considered when designing the exercise program, in order to achieve optimal benefits, greater participation, and adherence to exercise.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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