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Exercise interventions for patients with type 1 diabetes mellitus: A narrative review with practical recommendations

Martin-Rivera F *et al*. Exercise and type 1 diabetes mellitus

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INTRODUCTION

Type 1 diabetes mellitus (T1DM) is a chronic autoimmune disease that results from the immunological destruction of pancreatic insulin-producing β-cells, which can lead to micro (*e.g.*, retinopathy, neuropathy, and nephropathy) and macrovascular complications (*e.g.*, coronary arterial disease, peripheral artery disease, stroke, and heart failure) as a consequence of chronic hyperglycemia[1]. According to the International Diabetes Federation (IDF) and World Health Organization (WHO), 25-45 million adults (> 20 years old) suffer from T1DM worldwide[2]. In addition, it is estimated that the number of people with T1DM in the world will increase 25% by 2030[3].

Despite the widely available and compelling evidence that regular exercise is an efficient strategy to prevent cardiovascular disease and to improve functional capacity and psychological well-being in people with T1DM, over 60% of individuals with T1DM do not exercise regularly[4,5]. Lack of time, fear of a hypoglycemic event, and loss of glycemic control due to inadequate knowledge of exercise variable management, are the main barriers to increasing physical activity in patients with T1DM[6]. It is, therefore, crucial to devise approaches to motivate patients with T1DM to exercise, and to adhere to a training program, as well as to inform them of the specific characteristics of the training program (*e.g.*, exercise mode, intensity, volume, frequency). Moreover, given the metabolic alterations that occur during acute bouts of exercise in T1DM patients, exercise prescription in this population should be carefully analyzed to maximize benefits and to reduce potential risks.

AEROBIC EXERCISE AND T1DM

Aerobic exercise guidelines and benefits

Aerobic exercise is defined as continuous physical exercise of moderate intensity (50%-70% of maximum heart rate) and of high volume (> 20-30 min), which involves large muscles and requires the presence of oxygen to obtain energy[7]. Examples of this exercise mode are cycling, swimming, walking or running performed at moderate intensity[7]. This type of exercise has traditionally been recommended for specific populations, such as T1DM. In fact, the American Diabetes Society recommends at least 150 min, per week of aerobic exercise for the better glycemic regulation and improvement of the disease[8].

Aerobic exercise has positive effects on T1DM patient health, improving insulin sensitivity, body composition, endothelial, pulmonary, and cardiac function, as well as cardiorespiratory fitness[7] (Figure 1). It is thus, obvious that aerobic exercise training may robustly protect people with T1DM from several complications associated with cardiovascular disease, the main cause of mortality and morbidity in this population[9].

Aerobic exercise in T1DM population: general considerations

T1DM patients must consider various factors before performing continuous moderate-intensity exercise safely. Before starting the training program, certain factors must be considered. Patient's physical condition level/capacity, previous exercise experience, the duration and intensity of the current exercise, blood glucose at that given moment, the dose of pre-exercise administered insulin, and finally the general diet in the preceding period[4,10]. Exogenously administered insulin allows glucose to enter into muscle cells, consequently generating the energy to maintain movement, since the entire metabolism during and after any given exercise will be altered.

During aerobic exercise, blood glucose enters the muscles to meet the needs for increased energy generation, in the presence of oxygen initiating aerobic glycolysis. Physical exercise can increase muscle glucose demand and consumption up to 50-foldthrough an increase in insulin sensitivity and an increase in insulin-independent muscle glucose transport[11]. Thus, insulin secretion in people without T1DM pathology is reduced. This happens, precisely, to compensate for the increase in insulin sensitivity and glucose transport caused by physical exercise itself, so the reduction in blood insulin does not restrict the supply of glucose to the muscles[4].

Nevertheless, to maintain metabolic homeostasis and to avoid hypoglycemia, different mechanisms are activated that regulate blood glucose concentration. Four metabolic pathways are triggered to ensure energy production: (1) Glucose mobilization (from glycogen stores) from the liver; (2) fatty acid mobilization from adipose tissue; (3) gluconeogenesis (production of new glucose molecules) from non-carbohydrates (CHO) precursors (amino acids, lactate and glycerol); and (4) blocking glucose entry into cells and promoting fatty acids (alternative: Oxidation for energy generation) to be used in energy generation[12]. These mechanisms are orchestrated by glucagon, cortisol, growth hormone (GH), epinephrine, and norepinephrine. When blood glucose concentration decreases, these hormones respond by activating mechanisms to restore this imminent hypoglycemia: glucagon increases liver glucose production and stimulates gluconeogenesis while cortisol-GH balance stimulates gluconeogenesis and fatty acid mobilization. Epinephrine and norepinephrine (catecholamines) are responsible for the catabolism of glycogen (glycogenolysis) and lipids (lipolysis) and for reducing muscle glucose consumption. On the other hand, norepinephrine reduces insulin secretion so that it does not interfere with the increase in blood glucose caused by the aforementioned hormones[13].

Important differences in the metabolic behavior of T1DM patients during aerobic exercise must be considered. Furthermore, physical exercise response depends on exercise intensity and volume, CHO intake, as well as type and amount of exogenous insulin[4]. Unlike in the healthy population, during aerobic exercise in T1DM patients, exogenously insulin cannot decrease similarly to the pattern of non-T1DM individuals, the latter due to non-insulin-dependent muscle glucose transport and insulin sensitivity increase[11]. Moreover, given the pharmacokinetics and peak action of exogenous insulin and considering that exercise intervention is usually performed between 0-4 h after insulin injection, insulin levels are unpredictable. In addition, especially when injected near currently active musculature, insulin can be rapidly absorbed by subcutaneous tissue, rapidly transferring it into the bloodstream when exercise activity is initiated, with unforeseeable results[12].

The abnormally high blood insulin levels during physical exercise in T1DM, result in an exaggerated entry of glucose into the musculature and the inhibition of endogenous glucose production and fatty acid mobilization mediated by cortisol, GH, glucagon and catecholamines. Under normal conditions, these hormones act by increasing blood glucose concentration in the face of low insulin levels, but in T1DM these hormonal mechanisms are impaired[4,12]. Consequently, an excessive drop in blood glucose concentration or even, sheer hypoglycemia (< 70 mg/dL) may occur during physical exercise, which, depending on its severity, can cause dizziness, fainting, and even coma. Such hypoglycemic events can still occur hours after the end of physical exercise if appropriate measures are not undertaken.

After physical exercise, muscle glucose consumption is reduced, but insulin sensitivity remains high. This fact, together with the need to replenish muscle glycogen stores that have been consumed during physical exercise, can lead to post-exercise hypoglycemia and even occur while asleep at night, as insulin sensitivity tends to be biphasic: occurring immediately after physical exercise and 7-11 h later. People with T1DM may potentially experience between 42 and 91 hypoglycemic episodes annually. Moreover, approximately 12% of T1DM patients have at least one severe hypoglycemia episode per year[14]. The fear of these episodes makes people with T1DM unwilling to participate in this type of exercise[15].

In summary, the appropriate course of action for people with T1DM in order to be able to safely engage in aerobic physical exercise is based on ensuring an adequate CHO intake, prior to physical exercise, that elevates blood glucose levels to above 126 mg/dL but not over 270 mg/dL, in tandem with a reduction of insulin dosage before training, to counteract the increase in insulin sensitivity and the intensification of non-insulin dependent glucose transport mechanisms occurring during physical exercise[4]. To this end, it is important to take at least two blood glucose measurements, one half an hour before and a second 10 min later. If the physical exercise is long-lasting, an extra supply of glucose and fructose will be essential during the exercise. After the end of physical exercise, insulin reduction and CHO intake is again essential to prevent post-exercise hypoglycemia[16].

When the adjustment in insulin dose and CHO intake becomes imbalanced, diabetic ketoacidosis may succeed. In the presence of a reduced insulin levels and a high concentration of counter-regulatory hormones such as epinephrine or glucagon, glucose is unable to enter the muscles, among other tissues, and as a result, non-esterified fatty acids and glycerol are produced from the catabolism of triglycerides. Glycerol is used as a substrate in gluconeogenesis, but fatty acids, catalyzed by carnitine, are oxidized to ketone bodies in the liver, as an alternative means of obtaining energy. Hyperketonemia may lead to serious health sequalae[17] such as dizziness, vomiting, nausea, while when severe, cerebral edema or myocardial injury may result. It is therefore imperative to adjust insulin dosages suitably to ensure a safe exercise activity and avoid complications due to either excess or deficiency of the hormone[18].

High-intensity interval training and T1DM

High-intensity interval training (HIIT) is a type of physical exercise with a recent increase in popularity among fitness enthusiasts (ranked in the top 3 of world fitness trends)[19] and sport science academics alike, with almost 700 publications in PubMed. Despite this recent surge in acclaim, HIIT modalities have been employed in sports performance training since the 1920s[20]. HIIT's physiological impact has recently been informed in both clinical and sport contexts[21]. HIIT presents a unique opportunity to obtain cardiorespiratory and metabolic benefits, comparable to those obtained by classic moderate-intensity continuous training[22], trough lower training volumes, addressing the main barrier cited by most people for not doing physical exercise: Lack of time. HIIT consists of performing short-to-moderate (between 8 s and 4 min) bouts of any given physical exercise (mainly endurance exercises) at high intensity (*i.e.*, above the anaerobic threshold), interspersed by brief resting intervals performing low intensity activities such as walking or passive rest periods (ranging from 4 s to 60 s)[23].

Several different HIIT protocols have been proposed throughout the scientific literature based on: Exercise type, exercise intensity, volume (time duration) and number of exercise intervals, intensity and duration of rest periods, number of sets, length of each set, rest between sets, and exercise intensity during active rest periods[24]. Despite the high variability observed, the considerable majority of HIIT protocols use high intensity exercises intervals performed between 10 s and 4 min with 30-60-s rest periods between sets. These training programs pursue the accumulation of short bouts of high intensity exercise (> 90% of VO_{2max}) otherwise not sustainable for long time periods, interspersing short resting periods, that allow the high-exertion intervals to be completed at the desired intensity. A complete standard HIIT session usually takes/requires between 20-40 min, including rest periods, of which at least 4 min must be at high intensity (considering the sum of all intervals)[20,25,26].

HIIT's primarily anaerobic energy production, as high intensity intervals are usually performed above 90% of VO_{2max}, where the initial substrates used are free ATP in the muscle fiber and phosphocreatine, determine the acute responses in relation to the metabolism and endocrine system. An aerobic component is also necessary, as recovery intervals depend on it[27]. Hence, HIIT has been lately proposed as a potentially effective tool to improve blood pressure, weight control, glucose regulation, cardiorespiratory fitness, and psychological well-being in chronic pathologies such as hypertension[28], obesity[29], metabolic syndrome[30], T2DM[31], heart failure[32], chronic obstructive pulmonary disease[33], and also mental illness[34]. However, despite the benefits HIIT has demonstrated in other chronic diseases. The effect that this type of training has on people with T1D has not yet been extensively studied[4].

High intensity stimuli lead to an increase in catecholamine secretion, inhibiting insulin-mediated glucose consumption and accelerating gluconeogenesis. As a result, obtaining energy from glucose without the intervention of oxygen (anaerobic glycolysis), muscle fiber and blood lactate concentrations increase. This process also inhibits insulin-mediated glucose consumption and promotes glucose production by the liver. Taken together, these mechanisms contribute to a much safer glycemic regulation during and after physical exercise in people with T1DM compared with moderate-intensity aerobic exercise, preventing the occurrence of hypoglycemia[1]. In addition, oxygen consumption remains elevated and helps the subject to revert to a regular basal metabolic state after training through lactate clearance, increased cardiopulmonary function, increased body temperature, enhanced catecholamine effect, and glycogen re-synthesis, using lipids as an energy substrate[35].

Despite being an exercise mode that has been little studied in the T1DM population, HIIT seems to have positive cardiovascular and metabolic effects in people with this condition. Reported benefits include increases in VO_{2max}, improvements in vascular function, psychological well-being, body composition, cardiac function, antioxidant and anti-inflammatory markers, along with a reduction in the amount of insulin administered[36-41] (Figure 1). All the above, along with the prevention of hypoglycemia and the short time required, can overcome the major barriers that people with T1DM present against physical exercise[6,15], positioning HIIT interventions as a useful therapy for this spectrum of population, instead of aerobic or resistance exercise training, which pose higher risk of hypoglycemia and require more time, although they are not mutually exclusive.

RESISTANCE TRAINING AND T1DM

Resistance exercise guidelines and benefits

Resistance exercise refers to the exercise mode in which muscles produce tension to accelerate, decelerate or maintain immobility for any given resistance. This resistance could be weights, bands, or even the subject's own bodyweight working against gravity[42]. Depending on training variable manipulation (exercise volume, intensity, mode of contraction, movement velocity, and rest intervals between sets), a specific resistance training program might result in muscle hypertrophy, strength, mechanical power and endurance enhancements[43]. Resistance training is currently being recommended for T1DM by the American Diabetes Association and the American College of Sports Medicine, preformed in 2-3 non-consecutive training days prioritizing large muscle groups, with at least 8-10 exercises in 1 to 3 sets of 10-15 repetitions, at an intensity ranging from 50% to 75% of one-repetition maximum (1RM)[12,44].

There is a known relationship between skeletal muscle mass and higher-level functional capacity[45]. People with T1D are susceptible to muscle mass loss and sarcopenia faster than people without this disease, even without having developed disease-specific complications[46]. Resistance training might therefore address those fundamental deficits in this population[47]. Apart from muscle mass increase, one of the main benefits of resistance training in T1DM patients is the improvement of bone density, essential in this population since, due to hyperglycemia, T1DM patients experience bone mineral mass loss earlier than people of the same age, physical condition, and body composition[48,49]. It is also well-known that resistance training improves body composition (*i.e.*, reduced fat mass and increased muscle mass)[50], thus, preventing the development of overweight, lately noted as a prevalent issue in this population[51] (Figure 1). In addition to the significant improvements observed in functional capacity after accomplishing a resistance training program, another fundamental benefit of resistance training is its impact on cardiovascular health through the improvement in lipid profile and vascular function[50]. This is relevant for T1DM patients since cardiovascular disease is the leading cause of mortality in this population[52,53]. Moreover, an adequate resistance training program enhances functional capacity by improving daily activity functionality, preventing falls, injuries and cardiovascular diseases, and increasing independence[12,50].

Despite the lack of studies analyzing the acute response to resistance training in people with T1DM[50], it should be noted that hormonal response and the overwhelmingly anaerobic metabolism cause a much slower reduction in glucose levels during resistance training than that occurring during aerobic exercise in people with T1DM. Similarly, resistance training is associated with a much more stable post-exercise glucose concentration in comparison to aerobic exercise (hypoglycemia during and after exercise), which would be reduced with this exercise mode[54]. The increases in catecholamine concentration during resistance training and consequently the increase in endogenous glucose production, lead T1DM patients to adjust exogenous insulin dosage and CHO intake much easier than with aerobic exercise. However, certain types of resistance training with high volume and low intensities, might induce a decreased hormonal response, but resistance training with sufficiently high intensity and low volume, is associated with an enhanced hormonal response, leading to a higher hepatic glucose production. Moreover, an initial reduction in exogenous insulin or CHO intake before the resistance training program to prevent the drop in blood glucose drop is not necessary, as opposed to what typically occurs with aerobic exercise. Despite this, it may still be necessary to control the hyperglycemic tendency after resistance exercise, increasing the insulin dose, and postponing the intake of CHO[4]. However, the acute effect of resistance training in people with T1DM has not been elucidated yet, and more research is warranted to understand the specific underpinning mechanisms of the insulin/CHO ratio, in association with different types of resistance training completed[14,50] (Figure 1).

PRACTICAL APPLICATIONS

Conditional and psychological assessment

A comprehensive pre-exercise screening should be performed before designing an individualized training program for each T1DM patient. This should be preferably performed by sports science professionals with proper expertise in T1DM. Prior evaluation should include an anamnesis assessment and physical examination, as well as a cardiopulmonary function test. Patients should also be screened for risk factors or presence of cardiovascular, respiratory, or metabolic disorders apart from T1DM. When the medical approval for the implementation of an individualized training program has been obtained, the patients' cardiorespiratory, neuromuscular and functional performance should be tested (Table 1). Similarly, it is important to use tools to assess important psychological aspects such as quality of life and sleep quality, since these are issues that can affect people with T1DM (Table 1).

Practical recommendations for exercise prescription in T1DM patients

The individualized exercise program should be designed to address the patient's goals (*e.g.*, improve strength, endurance, balance, coordination, *etc.*) considering patient's baseline impairments and capabilities. The exercise program should include all the necessary training variables, such as frequency, volume, intensity, exercise mode, and precautions to be considered, prior to and after the program. It is important to bear in mind that, in practice, blood glucose levels may show a variable response for the same CHO-insulin adjustments, a multitude of factors, such as the food previously eaten, hours of sleep, stress, exert differing influence. As a consequence it is necessary that, blood glucose should be analyzed in each training session, and necessary actions should be taken. At times, it will be necessary to adapt the training to the expected behavior of blood glucose. For example, if a patient with T1DM has forgotten to lower the pre-training insulin dose and aerobic exercise was planned, it will be necessary to modify the training to high-intensity interval work to compensate for the drop in blood glucose that would have occurred with aerobic exercise. On the other hand, if insulin adjustment has not occurred or the patient is at high blood glucose values without circulating insulin, intense resistance training or HIIT should be substituted by aerobic tasks. General recommendations for practical application are shown in Table 2.

Patient's previous experience and training status must be considered when designing any training program. In the first training weeks focus on basic general conditioning to improve technique in basic resistance exercises, such as squats, lunges, deadlift, other press and pull movements, while first adaptations to resistance training are acquired with simple exercises (*e.g.*, weight-stack machines or exercises performed with simple materials such as elastic bands). Simultaneously, HIIT performed with low-impact exercises, such as cycling or rowing, is an excellent option, since this does not require significant insulin-CHO adjustments and is safe for the lower limb joints. It is essential, as well, that the person increases daily activities (*e.g.*, taking the stairs, walking as much as possible, reducing sitting time). Moreover, before each training session, a warm-up consisting of unloaded pedaling or cranking, general joint mobility and dynamic stretching should be performed. Controlling daily load by quantifying total training session rating of perceived exertion as well as glycemia levels before each session is recommended.

The ideal scenario would involve the use of continuous glucose monitoring (CGM), a relatively new technology that provides real-time knowledge of intra-session and inter-session glucose regulation[55]. Since glucose does not have a mathematical behavior, this technology is of great importance to prevent adverse events during exercise training and in the subsequent hours. In the same way, insulin pumps help to automatically regulate the exogenous administration of this hormone and therefore to maintain stable glucose levels, depending on exercise and diet. However, accessibility to CGM is limited in real scenarios. Hence, it is important to analyze hormonal and metabolic responses to each type of exercise in patients with T1DM, in order to control pre- and post-exercise insulin administration, as well as CHO intake.

CONCLUSION

Aerobic and resistance exercise are safe and effective training methods in T1DM patients. Current evidence has shown that a supervised and individualized exercise program with aerobic exercise performed 1-3 times/week, including low-volume high-intensity exercise training along with 1-3 sessions per week of resistance training, is sufficient to improve physical fitness, functional capacity, quality of life and mental health in this population. These guidelines should be adapted according to the patient's needs, abilities and preferences.

Figure 1 Main benefits of aerobic training, high-intensity interval training and resistance exercise in type 1 diabetes mellitus patients. HIIT: High-intensity interval training.

Table 1 Evaluation protocols in type 1 diabetes mellitus exercise programming

Parameter	Measures	Comments
Aerobic fitness		
Incremental test	Workload and steady-state HR to predict V_{O2peak}; RPE	Treadmill or cyclo-ergometer; Gas collection system and HR monitor necessary. Begin with unloaded warm-up
6-min walking test	Total distance walked, HR, RPE, BP	HR and BP monitor necessary
Muscular strength/power		
Indirect repetitions maximum testing	Maximal weight lifted for < 10 repetitions	Use machines. Remind patients to exhale on concentric action and avoid holding their breath
Force-Velocity profile	Execution velocity at a given load	Encoder necessary
Timed up and go test	Time to stand from a chair, walk a 3-m round trip, and sit back down on the same chair	Results correlate with gait speed, balance, functional level, the ability to go out
30-s sit to stand test	Number of times patient comes to a full stand with arms crossing a standard size chair in 30 s	A functional measure of lower limb strength, power, and muscle endurance
Flexibility/mobility		
Goniometry	Range of motion	Focus on flexibility of hamstrings, hip flexors, ankle plantar flexors, shoulder adductors, and internal rotators

WBLT	Ankle dorsiflexion	No footwear; no equipment
Psychological well-being		
SF-36	Quality of life	Eight-domain profile of functional health and well-being scores
PSQI	Sleep quality	Seven-domain profile of sleep quality and related disorders

BP: Blood pressure; HR: Heart rate; PSQI: Pittsburgh Sleep Quality Index; RPE: Rating of perceived exertion; SF-36: Short Form Health Survey-36; WBLT: Weight-bearing lunge test.

Table 2 Practical recommendations for exercise prescription in type 1diabetes mellitus patients

Aerobic exercise[1]	HIIT	Resistance exercise
Exercise intensity: Start with an intensity of 40%-70% of VO_{2max} and gradually increase to 60%-80% of maximum heart rate. A perceived exertion scale (rating of perceived exertion, RPE) of 11-13 is recommended	**Exercise intensity**: > 90 VO_{2max}, 90%-95% of maximum heart rate, and a RPE of 15-18	**Exercise intensity:** 50%-75% 1RM, RPE of 7-8. Participants should perform the exercises as fast as possible during the concentric phase (maximal movement intention). A 20% loss in concentric velocity among the repetitions of each set may be established as a limit in the volume at the given intensity
Exercise volume: 10-40 min duration is suggested. At first, it can be divided into three bouts of 10-12 min per session	**Exercise volume**: 12-20 sets. Bouts of 30 s interspersed by 60 s rest (ratio 1:2)	**Exercise volume:** 1-3 sets of 10-15 reps; 8-10 exercises of large muscles are essential
Exercise mode: Low impact cyclo-ergometer, arm ergometer, arm-leg ergometer, aquatic exercise, treadmill walking, rowing, and running	**Exercise mode**: Aerobic exercises such as cycling, running, rowing, *etc*. Firstly, HIIT must be performed in low impact conditions as cyclo-ergometer or aquatic environment, aiming at least a total of 4-min at high	**Exercice mode:** Prioritise lower limb exercises and multi-joint exercises. Exercise velocity must be initially moderated (1-2 s concentric- 1-2 s eccentric)

	intensity	
Training frequency: 1-3 sessions per week; as per patient tolerance	**Training frequency**: 1-3 sessions per week	**Training frequency:** 2-3 sessions per week
Progression: During the first 1-4 mo, progression should be achieved by increasing the duration or frequency of exercise sessions. After this time, test whether higher intensity in continuous exercise is tolerated	**Progression**: Increase total training volume gradually, then increase the density by reducing active rest intervals or increasing the length of the HIIT bouts, as per patient tolerance	**Progression**: Begin with weight-stack machines, elastic bands and weightbearing exercises. Increase load and progress to more technically demanding exercises. An exercise intensity of resistance can be securely added by 2% to 5% when 15 repetitions can be properly performed in successive training sessions

[1]When the insulin-CHO ratio is cautiously established.

HIIT: High-intensity interval training.

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