Sports Medicine

Chapter 4

Physical Activity in Diabetes

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1. Why Physical Activity in Persons With Diabetes?

Physical activity is one of the cornerstones for the prevention and treatment of many noncommunicable diseases (NCDs), according to the World Health Organization [1]. Diabetes is one the main NCDs, besides official Organizations and Scientific Associations states the importance of physical activity for all the groups of people with diabetes [2-4].

Diabetes mellitus (DM) is a very prevalent disease, numbering 463 million people in worldwide in 2019 and projected increase to 700 million in 2045, according to the International Diabetes Federation [5]. DM is classified in different groups, specially according to the etiology. Type 2 diabetes (T2D) is the most prevalent, reporting about 90% of the diabetes. T2D affects about 9.3% of the world's population and its prevalence is increasing worldwide. It is considered a multisystemic disease characterized by a relative insulin deficiency caused by pancreatic β-cell dysfunction and insulin resistance (IR) in target organs such as the liver, adipose tissue, muscle and, the brain [6]. Over time, inadequate production of insulin can develop as a result of pancreatic β-cells failure to keep up with demand [5]. This type of diabetes is more frequently found in older adults, but is mainly associated with being overweight or obese, sedentary lifestyle, poor quality of diet, and also with a family history of diabetes [7, 8].

Type 1 diabetes (T1D) is the second most frequent, accounting for approximately 5 to 10% of diabetes diagnosis [7, 9]. T1D results from progressive cellular-mediated autoimmune destruction of the pancreatic β-cell that leads to complete insulin deficiency. Patients with

T1D require exogenous insulin to survive. Frequently, these patients have the diagnosis when they are young, and it is not associated with weight, unhealthy diet or sedentarily lifestyle; the patients are usually normal weight and have physical activity habits, perform some of exercise or even a competitive modality.

Another prevalent type of diabetes is gestational diabetes mellitus (GDM), which usually exists as a transient disorder during pregnancy and resolves once the pregnancy ends [5]. For many years, GDM was defined as any degree of glucose intolerance that was first recognized during pregnancy. However, according to the American Diabetes Association (ADA), this definition has limitations since several times cases of GDM represent preexisting hyperglycemia that is detected by routine screening in pregnancy. This fact gains more importance with the evidence of the increasing rates of obesity, prediabetes or undiagnosed T2D in recent decades [7]. As in T2D, GDM is associated to obesity, previous GDM and with age [5]. There are some other causes of diabetes representing a small percentage of the total and are related to different conditions, such as monogenic diseases, diseases of exocrine pancreas, chemicals or drug-induced diabetes.

People living with diabetes have a higher risk of morbidity and mortality than general population. Long-term uncontrolled diabetes can cause several complications mainly related with macrovascular complications as premature atherosclerotic cardiovascular disease, cerebrovascular diseases, and microvascular complications manifested as retinopathy with potential loss of vision, nephropathy leading to renal failure, peripheral neuropathy with a high risk of foot ulcers and amputations [5]. Before insulin was discovered in 1921, exercise was considered a dangerous activity, usually discouraged because of the high risk of metabolic disorder that could be precipitated. Currently, exercise is not only considered safe, but is prescribed as a basic treatment of the disease, essential for a healthy lifestyle and recommended for all patients with diabetes. The beneficial effects of regular physical exercise associated with diabetes are numerous, offering the population an improvement in physical capacity, a decrease in cardiovascular risk and an increase in emotional and social well-being [10].

2. What are the Hormonal and Molecular Mechanisms Induced By Exercise?

The effect of exercise on blood glucose levels is determined by the interaction that takes place between metabolic and hormonal effects, as well as changes produced in muscle glucose uptake. The metabolic responses to different forms of exercise are distinct. However, in almost all forms of exercise, regardless of the intensity or duration, blood glucose concentrations are normally held within a tight range (4–6 mmol/L or 70–110 mg/dL). During aerobic exercise, insulin secretion decreases, and glucagon secretion increases in the portal vein to facilitate release of glucose from the liver to match the rate of glucose uptake into the working muscles [11].

2.1. Energy substrates during rest and exercise

Fat deposits of adipose tissue are the major source of energy in the human body, with a reserve of between 60,000 and 150,000 kcal. This content is much greater than the energy that carbohydrates can provide, approximately 2,000 kcal. Most of these, about 1,500 kcal, are stored as glycogen in the muscles, and the rest comes from glycogen deposits accumulated in the liver and from glucose found in the blood and extracellular fluids. During the early stages of exercise, muscle glycogen is the main source of energy for muscle contraction. Subsequently to the depletion of muscle glycogen deposits, lipolysis of fatty acids stored in adipose tissue is activated. Thus, the increase of free fatty acids and glycerol in plasma constitutes an additional source of energy for muscle contraction [12,13]. Glucose will then be provided by hepatic glycogenolysis followed by hepatic gluconeogenesis. The substrates used by the liver to synthesize new glucose are lactate, pyruvate and certain amino acids, mainly alanine, together with the glycerol derived from the metabolism of triglycerides. The contribution of different substrates depends on the intensity, duration and kind of exercise performed. The relative proportion of each pursues to maintain three fundamental physiological aspects: 1) to preserve blood glucose, 2) to maintain the efficient metabolism and storage of glucose, and 3) to preserve and maintain deposits of muscle glycogen to avoid and/or delay the onset of muscular fatigue.

2.2. Endocrine and metabolic response to exercise

Metabolic adjustments to exercise are possible thanks to a highly efficient system that integrates nerve impulses and hormonal response. During rest, individuals without diabetes unveil a basal insulin secretion, which increases in response to the rise in blood glucose that occurs after ingesting of food. It is well known that insulin stimulates glucose uptake by skeletal muscle and by the liver, to later facilitate its storage in the form of glycogen. Exercise causes nerve stimulation, acting on pancreatic β-cells and leading to inhibition of insulin secretion [14, 15]. This decrease in insulin levels does not affect muscle glucose uptake, as exercise triggers other mechanisms that can improve muscle glucose uptake. Stimulation of another pancreatic hormone, glucagon, and, in particular, its close and proper interaction with insulin, are phenomena taking place during the exercise that are essential to maintaining and regulating glucose production. Decreased insulin levels at baseline exercise promote increased glucagon secretion by alpha cells in pancreatic islets. This increase is critical and acts directly on the metabolic pathways of hepatic glucose production (glycogenolysis and gluconeogenesis). Also, during exercise, counter-regulatory hormones increase, such as catecholamines, cortisol and growth hormone, promoting the balance of the aforementioned metabolic pathways and increasing lipolysis in fat cells. High-intensity exercise can activate these counter regulatory hormones in an exaggerated way, resulting in a noticeable increase in hepatic glucose production and a moderate degree of hyperglycemia when exercise is over.

2.3. Effects of insulin and exercise on muscle glucose uptake

Both insulin and muscle contraction help glucose enter the muscles, where it is oxidized and subsequently turned into energy for muscle contraction. However, the mechanisms by which these two stimuli facilitate glucose transport are not entirely understood. There is evidence suggesting that they do not act in a similar manner. For example, exercise, unlike insulin, induces an increase in muscle blood flow and glucose transport, which persists for hours after exercise has ended. Experiments with laboratory animals have demonstrated that the induction of glucose transport produced by exercise is independent of insulin, as tyrosine kinase activity of the insulin receptor is not stimulated. Instead, it appears to act through other pathways, in particular, those involving the AMP kinase (AMPK). Molecular characterization of glucose transporter GLUT 4, which is specifically expressed in muscle and fat cells, has shed new light on elucidating the mechanisms mentioned above. It appears that the translocation of GLUT 4 from the cytosol to the cell membrane is one of the main mechanisms of glucose transport in muscles and can be stimulated both by insulin and by exercise [16].

The existence of another type of transporter in muscle, GLUT 1, has also been demonstrated, although its function is not entirely known. The important role of certain enzymes such as hexokinase and glycogen synthase also highlight the complex system of glucose transport into muscles. AMPK [7] emerges as an important molecule regulating multiple metabolic processes that occur in skeletal muscle, in response to exercise. It appears that muscle contractions induced by exercise increase the activity of the enzyme, which, in turn, stimulates glucose transport [18, 19].

2.4. Skeletal muscle as an endocrine organ

The hypothesis of muscle having an endocrine-like effect on distant tissues was first proposed by Pedersen and colleagues [20, 21]. Skeletal muscle has been identified as an endocrine organ, which has the capacity to produce and secrete myokines, substances derived from skeletal. Myokines have been suggested to mediate anti-inflammatory and metabolic effects [22]. Even it is postulated that myokines contribute to mediate the preventive effects of exercise against chronic diseases, such as cardiovascular diseases, T2D, cancer, and dementia [23, 24]. It is well known that myokines exert their effects on, cognition, lipids and glucose metabolism, browning of white fat, bone formation, endothelial cell function, hypertrophy, skin structure, and tumor growth. Then it is postulated that the identification of new myokines and their specific roles may lead to novel therapeutic targets for several diseases [25].

IL-6 was the first well documented myokine that is produced and released from muscle cells during exercise. IL-6 exerts direct metabolic effects on pancreas as it stimulates β-cell proliferation, prevents apoptosis caused by metabolic stress, and regulates β-cell mass *in vivo* [26,27]. Irisin was later identified [28] as a novel contraction-induced myokine by which exercise could increase basal energy expenditure and result in weight loss and improved glucose metabolism. However, the study was criticized by various groups, that have not been able to find irisin in human circulation [29]**.** Nonetheless, a new published study using mass spectrometry strongly supports the existence of circulating irisin in humans [30]. IL-15 has pleiotropic effects in the immune system, in skeletal muscle, and in regulating lipid and glucose metabolism [25]. In addition, it has been reported that exercise-induced IL-15 has a role in reducing skin aging [26].

2.5. Exosomes as vehicles of interorgan crosstalk

Accumulated evidence suggests that muscle and other tissues have an endocrine function and release peptides, metabolites and nucleic acids into the circulation in response to exercise to mediate the multisystemic adaptations. In addition to the concept of myokines a new emerging proposal termed exerkines appears including all factors released in response to exercise (peptides, metabolites and RNA mainly miRNAs). Several authors propose [27] that many of the exerkines are released within extracellular vesicles (EVs) [28] and in particular exosomes that are important mediators of the intercellular communication process occurring in response to exercise in humans. In addition, it is proposed that exosomes isolated from athletes following exercise or exosomes bioengineered to incorporate one or many of known exerkines will be therapeutically useful in the treatment of obesity, T2D, and other aging associated metabolic disorders [29] (**Figure 1**).

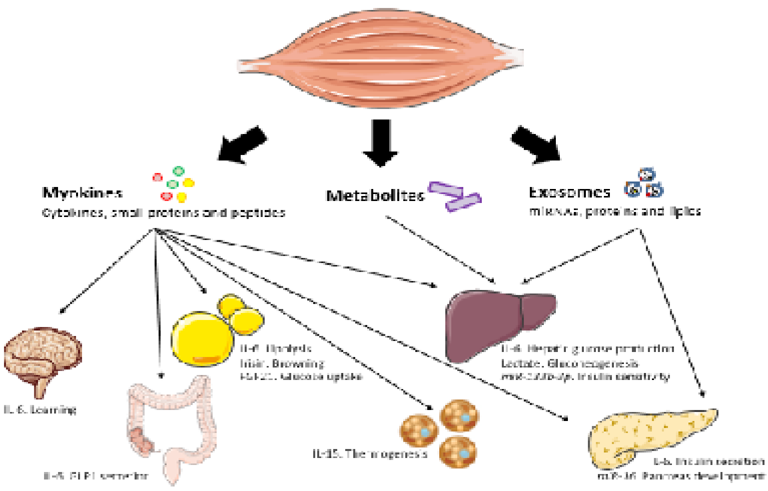

Figure 1: Skeletal muscle as an endocrine regulator of metabolism.

Skeletal muscle is an endocrine organ that, due to the release of myokines, metabolites or exosomal miRNAs, may influence metabolism in different organs by establishing cross-talk between tissues and having effects on several biological functions. (Illustrated by author C. Castaño)

It is well thought that the beneficial metabolic effects of exercise are mediated at least in part by the release of soluble factors by the muscles. Exosomes, small vesicles that facilitate the exchange of biological components among cells and tissues, may constitute one of these factors. A recent finding [30] demonstrate that exercise triggers the release of exosomes by the trained muscle in mice, carrying a specific miRNA signature that induces gene expression changes in the liver through downregulation of hepatic FoxO1, and contributing to increased insulin sensitivity. Importantly, treatment of sedentary mice with exosomes isolated from the plasma of trained mice improved glucose tolerance, insulin sensitivity and decreased plasma levels of triglycerides [30]. As a consequence, molecular characterization of exercise-induced exosomal miRNAs and their effects may drive the design of novel therapeutic strategies to alleviate insulin resistance and other aging-related conditions in an increasingly older society.

3. How is the Metabolic Response to Exercise in Patients With Diabetes?

Physical activity is essential for all people with diabetes, but different aspects should be considered for the benefits, as well as particularities in prescription. People with T1D are different from their non-diabetic counterparts, as they have an insulin secretion deficiency and, consequently, their counter regulatory hormones respond differently. Patients with diabetes treated with insulin should learn to mimic their own natural insulin secretory rhythm, in response to physiological changes induced by exercise. Any patient with diabetes and, especially, diabetic athletes should prevent problems arising from poor insulin dosage. If an athlete with diabetes starts exercise with a significant insulin deficiency, his/her response to exercise may trigger a hyperglycemic overcompensation, even ketosis, since a lack of insulin induces: 1) increased hepatic glucose production; 2) decreased peripheral glucose utilization; and 3) excessive lipolysis with an increase in free fatty acid production [2, 31].

In T2D the mechanisms or metabolic responses are different. In most cases of T2D, the main alteration resides in the action of insulin on the tissues, defined as insulin resistance. This alteration manifests itself through excess insulin production (hyperinsulinemia) and impaired glucose tolerance. Exercise has shown its remarkable qualities in the prevention and treatment of this defect. Thus its effects include the improvement of glucose transport into the cell (by acting independently of insulin) and the increase in insulin sensitivity in the transport of muscle glucose and in the production of glycogen from glucose. Physical training has been proposed as an intervention factor for the prevention and treatment of T2D and glucose intolerance [32].

There is extensive bibliography that provides evidence showing that physical training can generate weight loss in obese individuals, as well as improve the action of insulin in peripheral tissues and the risk of the metabolic profile. It has been shown that through a physical training program lipid oxidation and mobilization of muscle and liver glycogen stores are increased, improving the action of insulin on tissues. On the other hand, moderate training has been indicated as a therapeutic armament in T2D associated with insulin resistance, reducing postprandial hyperglycemia and overall glycemic control [33, 34, 35].

4. Benefits of Exercise for Diabetes

4.1. Prevention of diabetes

In the 2000s, several major clinical trials studied intervention with physical activity and/or diet for the prevention of T2D. One of the best known studies is the DPP - Diabetes Prevention Program, conducted with more than 3000 people with prediabetes [36]. For that study, 3 groups were randomized: lifestyle intervention (diet and 150 min/week of physical activity), metformin 850 mg twice daily, or placebo. After an average of 2.8 years of follow-up, the lifestyle intervention group was able to reduce the incidence of T2D by 58% compared to the placebo group. Another similar study, the DPS, achieved the same protection, reducing the incidence of T2D also in 58% with lifestyle intervention [37]. Da Quin Study and others also confirmed that physical activity is fundamental for prevention of T2D [4, 38, 39]. Despite many other benefits, there is no evidence that T1D could be prevented with physical activity.

The prevention of DMG through physical activity is based on smaller studies. For that, meta-analysis could demonstrate that physical exercise programs during pregnancy decreased the risk of DMG, particularly when the exercise program was performed throughout pregnancy. Furthermore, it was also observed decreases in maternal weight [40, 41].

4.2. Improvements in glycemic control

There are many studies and several meta-analysis demonstrating the importance of physical activity in the glycemic control in T2D. The simple act of walking, evaluated in a meta-analysis from 20 studies and 866 participants in structured programs, was able to reduce by 0,5% the HbA1c. Walking also reduced body mass index (BMI) and lowered diastolic blood pressure (DBP) [42].

Aerobic exercise alone or combined with resistance training improves glycemic control, systolic blood pressure (SBP), triglycerides, and waist circumference in T2D [43]. Two different meta-analysis demonstrated, in different modalities of aerobic exercise alone or combined with resistance training, significantly reductions of 0.6% in HbA1c [43, 44]. Several features of exercise can reduce HbA1c in T2D: the duration of exercise for more than 12 months (HbA1c -0.8% vs. -0.4%, if less than 12 months of exercise) [34]; the structured exercise of more than 150 minutes per week (HbA1c -0.89% vs. -0.36%, if less than 150 min per week) [45]; and also reduction of 0.22% in HbA1c in favor of high intense exercise compared to less intense [46].

Improvements in glycemic control associated with exercise are not as evident in people with T1D. Part of this challenge is due to the ongoing dynamic balance of the actions of different exogenous insulins, carbohydrate intake choices, and exercise modalities and duration (**Figure 2**). However, an important population-based study showed that those who engage in physical activity have better glycemic control (< HbA1c), need lesser insulin doses in addition to having higher HDL cholesterol and lower triglyceride values; they also have fewer severe diabetic events, such as hypoglycemic coma or ketoacidosis [47]. Furthermore, a meta-analysis confirmed the effects of exercise in improving glycemic control (reduction of 0.45% in HbA1c) and reduction of daily insulin dose, total cholesterol and, in a subgroup of studies with higher frequency (≥3 times/week) and longer duration (>12 weeks) of activities, also showed improved cardiorespiratory fitness (increases in VO_2max) [48].

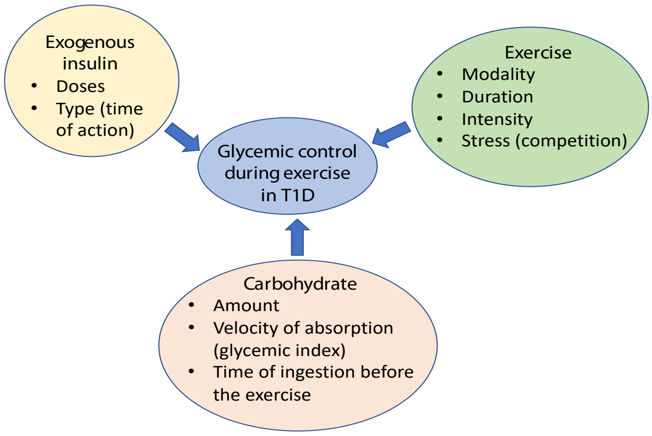

Figure 2: Factors involved in glycemic control during exercise in T1D.

4.3. Cardiovascular protection

Atherosclerotic cardiovascular disease (coronary heart disease, cerebrovascular disease, or peripheral arterial disease) is the leading cause of morbidity and mortality for individuals with diabetes, according to ADA [49]. For this, the care of the patients with diabetes must be focused on the sense of atherosclerotic cardiovascular disease prevention and protection. It was demonstrated that, even in patients with T1D in good glycemic control, CV mortality has double the incidence than in a similar population without diabetes [50]. This fact indicates that mere glycemic control is not enough for CV protection. In parallel, it was evident that mortality and incidence of cardiovascular outcomes decreased substantially among persons with T1D and T2D in the last years [51]. The study attributed these results to integrated care of patients with chronic disease, improved patient education in disease management, and advances in clinical decision support have likely reduced the rates of cardiovascular complications among patients with diabetes. Knowledge of risk factors and protective factors for cardiovascular disease is essential for cardiovascular protection in this population.

From the important lifestyle intervention studies, the Da Qing Diabetes Prevention Outcome Study, which now has 30 years of follow-up, it was able to support that lifestyle intervention (physical activity, diet, or both) can prevent or delay cardiovascular events and all-cause mortality in people with prediabetes [53]. In diabetes, the complications that cause most of the excess morbidity and mortality may occur mainly in subjects who have had longstanding diabetes, as long as 20-30 years. Therefore, long-term follow-up studies are needed to evaluate beneficial interventions, such as lifestyle changes.

An important prospective analysis that included 11,527 participants with T2D showed that a greater adherence to an overall healthy lifestyle (non-smoking, moderate to vigorous physical activity [≥150 min/week], high-quality diet, and moderate alcohol consumption) is associated with a substantially lower risk of CVD incidence and CVD mortality [52].

Another major study, the Look AHEAD, search for benefits of lifestyle intervention in established T2D [54]. Intensive lifestyle intervention focused on weight loss did not reduce cardiovascular events in overweight or obese adults with type 2 diabetes. Still, there was improvement in HbA1c and systolic blood pressure. However, a further analysis of the Look AHEAD study suggests an association between the magnitude of intentional weight loss and reduction in CVD incidence [55].

Observational studies of follow-up were able to demonstrate that exercise may reduce the risk of CV events in T1D. One study indicated the importance of the frequency and the intensity of exercise for the reduction of CV events [56], as well as other demonstrated a uncertain association with all-cause mortality (both sexes) and incident CVD (women only) [57].

4.4. Other diabetes complications protection

It has been postulated that physical activity has benefits also in preventing and delaying the complications related to diabetes. In the above-mentioned Da Quin study, lifestyle intervention in people with prediabetes delayed the onset of T2D and, in addition to the reduction in cardiovascular events, also reduced the incidence of microvascular complications and increased life expectancy [53].

Improvements on the endothelial function, insulin sensitivity and reduction of inflammation could be the responsibles for the reduction of kidney disease progression [58]. In individuals with T1D at risk of diabetic kidney disease (DKD) or with established DKD, regular moderate-to-vigorous physical activity was associated with reduced incidence and progression of DKD, as well as reduced risk of cardiovascular events and mortality. Since structured physical activity has great potential to enhance health and quality of life at all stages of chronic DKD, exercise advice and physical activity assessment should become an integral routine part of the patient-centered treatment strategy also in type 1 diabetes [58].

The results of a recent meta-analysis indicated that physical activity is associated with improved renal function in patients with diabetic nephropathy by increasing the glomerular filtration rate and decreasing the urine creatinine albumin rate. In addition, physical activity decreased the rate of microalbuminuria, the rate of diabetic nephropathy in patients with T1D, the rate of acute kidney injury, and the rate of renal failure [59].

A prospective and observational study included 2,639 patients with T1D from the ongoing nationwide multicenter Finnish Diabetic Nephropathy (FinnDiane) Study. Leisure-time physical activity (LTPA) was assessed by using a validated self-report questionnaire. Three hundred ten patients (11.7%) had chronic DKD defined as an estimated glomerular filtration rate of ≤60 mL/min/1.73 m2. Higher LTPA was associated with a lower risk of premature all-cause and cardiovascular mortality in patients with T1D. This study also demonstrated that physical activity is associated with a lower risk of mortality in patients with T1D and DKD [60]. The same group of researchers described also that frequent LTPA was associated with a lower incidence of severe diabetic retinopathy during the follow-up [61].

5. Modalities of Exercise and Physical Activity

5.1. Types of exercise

Initially, as definitions, *physical activity* is any form of muscular activity; namely, it is any movement a person executes. ***Exercise*** represents a subset of physical activity that is planned, structured, repetitive and intentional with a goal of improving or maintain fitness [62]. Both physical activity and exercise fulfill the objectives of benefits for diabetes. In the DPP Study, although weight loss was the most important factor to reduce the risk of incident diabetes, it was also found that achieving the target of at least 150 min of physical activity per week, even without weight loss, the incidence of T2D was reduced by 44%. Brisk walking was one of the modalities for that 150 min/week of moderate-intensity physical [63]. Moreover, simple acts as breaking up prolonged sedentary time may also be encouraged, as it is associated with moderately lower postprandial glucose levels [64].

Exercise, or physical activity, is generally classified as aerobic or anaerobic, depending on the predominant energy systems used to support the activity, although most exercise activities include a combination of energy systems. **Aerobic exercise** involves repeated and continuous movement of large muscle groups. Activities such as walking, cycling, jogging, and swimming rely primarily on aerobic energy-producing systems [2,31]. **Anaerobic training**, also called resistance or strength, includes exercises with free weights, weight machines, body weight, or elastic resistance bands for example. Resistance exercise can assist in minimizing risk of exercise-induced hypoglycemia in T1D. According to guidelines, when resistance and aerobic exercise are performed in the same exercise session, performing resistance exercise first results in less hypoglycemia than when aerobic exercise is performed first [2]. Several trainings have mixed aerobic and endurance compounds and it depends on the role or participation in a specific team sport, such as soccer or basketball, for example, that more aerobic or anaerobic system will be used. Likewise, **high intensity interval training (HIIT),** a modality that has been extensively studied in the recent years, also has aerobic and anaerobic components [31]. Specially in T1D, the glycemic control can vary depending on the modality of exercise, time expended and intensity. Hypoglycemia develops in most patients within about 45 min of starting aerobic exercise [31]. HIIT promotes rapid enhancement of skeletal muscle oxidative capacity, insulin sensitivity, and glycemic control in adults with T2D and can be performed without deterioration in glycemic control in T1D [2,65]. **Flexibility and balance exercises** are other important modalities due to the improvement of motion around joints, beneficial for gait and prevention of falls. Activities like tai-chi and yoga combine flexibility, balance, and resistance activities. Flexibility and balance exercises are very important for older adults with diabetes [2].

5.2. Recommendations

Each year, the American Diabetes Association (ADA) updates its recommendations for exercise or physical activity, according to the latest studies. The most recent recommendations indicate that [64] children and adolescents with T1D or T2D or prediabetes should engage in 60 minutes/day or more of moderate- or vigorous-intensity aerobic activity, with vigorous muscle and bone strengthening activities at least 3 days/week. Regarding adults, most with T1D or T2D should perform 150 minutes or more of moderate- to vigorous-intensity aerobic activity per week, spread over at least 3 days/week, with no more than 2 consecutive days without activity. For younger, more fit individuals, a shorter duration (minimum 75 minutes/week) of vigorous-intensity or interval training, HIIT, for example, may be an alternative. In addition to aerobic activities, it is recommended that adults with T1D and T2D to perform 2-3 sessions per week of resistance exercise on non-consecutive days. Women with preexisting diabetes, particularly T2D and those at risk for or presenting with GDM (as previous GDM, obesity and/or older ages), should be advised to engage in regular moderate physical activity prior to and during their pregnancies as tolerated. To a special group, older adults with diabetes, is recommended to train flexibility and balance 2-3 times per week. Yoga and tai-chi can be included according to individual preferences to increase flexibility, muscle strength and balance.

6. Controlling Exercise-Related Adverse Events in People With Diabetes

Regular exercise should be encouraged and supported by health-care professionals for many reasons, but primarily because the overall cardiometabolic benefits prevail over the immediate risks if certain precautions are taken. Safety measures should be considered to avoid exercise-induced adverse effects because physical activity does carry some potential health risks for people with diabetes, including acute complications like cardiac events, hypoglycemia, and hyperglycemia. A medical evaluation should be performed prior to the start of an exercise program in patients with complications from diabetes. In asymptomatic patients it is usually unnecessary as long as physical activity is low or moderate. It is essential to carry out a glycemic control prior to the start of any activity. Based on the results acquired, strategies will be proposed to achieve good control throughout the activity. Nutritional recommendations, adjustment of insulin dosage and drugs need to be enlightened by the clinical team. Specific recommendations and precautions will vary by the type of diabetes, age, type of exercise, and presence of diabetes-related health complications. For each individual, recommendations should be tailored to meet the specific needs [2].

6.1. Pre-exercise Evaluation

The consensus published by the American Diabetes Association for the screening of coronary artery disease concluded that routine testing is not recommended [66]. Moreover, no current evidence suggests that any screening cardiac protocol beyond usual diabetes care reduces risk of exercise-induced adverse events in asymptomatic individuals with diabetes [67]. Nonetheless, it is recommended that clinical team should perform a careful history, assess cardiovascular risk factors, and be aware of the atypical presentation of coronary artery disease. Undoubtedly, high-risk patients should be encouraged to start with short periods of low-intensity exercise and slowly increase the intensity and duration as tolerated. Clinical team should evaluate conditions that might contraindicate certain types of exercise or predispose to injury, such as uncontrolled hypertension, proliferative retinopathy, autonomic neuropathy, peripheral neuropathy, and antecedents of foot ulcers. Patients with complications may need a more thorough evaluation prior to starting an exercise program [64].

6.2. Exercise in the Presence of Microvascular Complications

The presence of chronic complications related to diabetes requires a series of adaptations in terms of the characteristics of each activity [68]. In the case of people with **peripheral neuropathy** in view of the diabetic foot, extreme care and revisions of the feet should be done, using appropriate footwear to avoid the risk of ulcers. When the patient has decreased pain sensation and a higher pain threshold in the extremities, the practice of some forms of exercise can result in an increased risk of skin lesions, infection, and Charcot joint destruction. Therefore, a thorough assessment should be done to ensure that neuropathy does not alter kinesthetic or proprioceptive sensation during physical activity, particularly in those with more severe neuropathy. It has been reported that 150min/week of moderate exercise improve outcomes in patients with prediabetic neuropathy [69]. All individuals with peripheral neuropathy should wear proper footwear and examine their feet daily to detect lesions early. The presence of **autonomic neuropathy** can cause hypotension, delayed gastric emptying as well as alterations in thermoregulation that should be considered throughout exercise. In addition, there is an alteration in the cardiac response to exercise. In fact, autonomic neuropathy can increase the risk of exercise-induced injury or adverse events through decreased cardiac responsiveness to exercise, postural hypotension, impaired thermoregulation, impaired night vision due to impaired papillary reaction, and greater susceptibility to hypoglycemia [70]. Cardiovascular autonomic neuropathy is also an independent risk factor for cardiovascular death and silent myocardial ischemia [71]. Therefore, individuals with diabetic autonomic neuropathy should undergo cardiac investigation before beginning physical activity.

When proliferative **diabetic retinopathy** or severe nonproliferative diabetic retinopathy is present, high-intensity exercise aerobic or resistance exercise should be contraindicated because of the risk of generating vitreous hemorrhage or retinal detachment. Consultation with an ophthalmologist prior to engaging in an intense exercise regimen may be appropriate [68]. Exercise is recommended in any type of **diabetic nephropathy**, always adapting the intensity to the physical abilities of each individual. Physical activity can acutely increase urinary albumin excretion. However, there is no evidence that vigorous-intensity exercise accelerates the rate of progression of renal failure, and there appears to be no need for specific exercise restrictions for people with nephropathy. It is recommended not to exercise the day before a protein test in urine, in order to avoid false positives.

6.3. Hypoglycemia

The risk of exercise-associated hypoglycemia is high in people with T1D, and it is therefore advisable to include exercise-related information in therapeutic education programs. People with T1D need to know the effects of different components of physical activity on blood sugar levels, as well as strategies to prevent glycemic fluctuations [2]. Aerobic exercise has a higher hypoglycemic effect than strength training or low volume of high-intensity exercise. Exercise duration and intensity are associated with increased muscle glucose consumption, and therefore an increased risk of hypoglycemia [72]. Performing aerobic exercise needs to be counterbalance by a higher carbohydrate intake before and throughout the activity. People with T1D should be instructed on the need to have carbohydrate-rich foods on hand, especially if they are exercising alone or playing sports in the mountains or at sea [73]. It is also necessary to increase carbohydrates intake and/or schedule a reduction in insulin doses up to 12-24 hours after exercise since muscle glucose uptake independent of insulin is still stimulated during the hours following activity, and muscles need more quantity of glucose to replenish glycogen stores [17, 74]. Hypoglycemia is less common in patients with diabetes who are not treated with insulin or insulin secretagogues, in these cases routine preventive measures to avoid hypoglycemia are not usually advised.

6.4. Factors that determine carbohydrate needs during and after physical exercise

Exercise-induced hypoglycemia is described as one of the main factors limiting physical exercise, as well as a cause of poor performance in athletes with type 1 diabetes. Though, certain strategies, such as supplementing carbohydrate intake, can reduce the severity and duration of these episodes, thereby eliminating the fear of exercise-induced hypoglycemia [75]. The role of carbohydrates in the diet of athletes with diabetes is important as a prerequisite for achieving maximum athletic performance, not only in improving and accelerating the recovery of energy stores in the body, but also in regulating blood glucose levels during training sessions and competitions. In general, the nutritional strategies used by athletes with and without diabetes should not differ. However, certain standards and guidelines must be established for including carbohydrate supplements within the set of specific treatments for diabetes [76].

The prediction of carbohydrates consumption during and in the hours after physical activity requires a great knowledge and analysis of factors specific to each type of activity. In this sense, the personal observations and experience of each individual are highly important. It is recommended to monitor blood glucose levels before and after exercise, or, if possible, to use a continuous glucose sensor. In general, the characteristics of the activity to be performed affect blood glucose levels to a high degree.

Type of exercise: Forms of exercise dominated by the aerobic component, such as walking, running, swimming, skating or cycling, produce greater glucose consumption and, therefore, have a stronger hypoglycemic effect. In contrast, forms of exercise with an elevated anaerobic component, like sprints, combat sports and working with heavy weights, can produce strong adrenergic stimulation (stimulating liver production of glucose) and thus usually have a lesser hypoglycemic effect post-exercise. Competitive sports can also be associated with significant emotional stress (high adrenergic stimulation), which causes increased blood sugar after exercise, especially in children and adolescents.

Duration: During the first 30-60 minutes of moderate- or high-intensity exercise, muscular and hepatic glycogen becomes the primary muscle fuel. Thereafter, the glycogen stores begin to decrease, and muscles increasingly obtain energy from fatty acids and glucose from blood. Succeeding these events is when the most significant changes in blood glucose are observed.

Intensity: Glucose is the preferred muscle fuel for exercise performed at a moderate or high intensity, whereas low-intensity exercise uses fatty acids as energy source. Therefore, low-intensity activities such as walking may have a minimal effect on blood sugar, whereas intense activities such as running could cause a stronger and faster blood glucose lowering effect.

Frequency: Hypoglycemic effects, especially after exercise, increase after several consecutive days of physical exercise. In this situation, since it is almost impossible to recover of glycogen stores from one day to another, the body is less able to use the mechanisms of hepatic glycogenolysis to regulate low blood glucose. Schedule: The timetable of insulin administration results in different blood insulin levels throughout the day, which give place a tendency to develop hypoglycemia during physical activity. This effect is more possible when exercise is performed just within 2-3 hours after rapid-acting insulin is administered.

Carbohydrates represent the main nutrient for both ensuring optimal muscle work and for maintaining blood glucose levels as close to normal as possible. Since reserves of carbohydrates in the body are limited, nutritional strategies must aim at maintaining or quickly replenishing these deposits once consumed through physical exercise [76].

6.5. Hyperglycemia

Exercise-induced hyperglycemia is more common in T1D. Overconsumption of carbohydrates before or during exercise, along with aggressive insulin reduction, can promote hyperglycemia during any exercise [77]. Intense exercise such as sprinting or heavy power lifting may promote hyperglycemia, especially if blood glucose levels are elevated when starting [78, 79]. A low dose of insulin can be administered to correct postexercise hyperglycemia taking in consideration that excessive insulin corrections after exercise may increase nocturnal hypoglycemia risk with devastating consequences for the individual [80]. Patients with T1D should test for blood ketones if they have unexplained hyperglycemia (≥250 mg/dL). In this situation, exercise should be delayed or suspended if blood ketone levels are elevated (≥1.5 mmol/L), as blood glucose levels and ketones may rise further with even mild activity and in this situation a serious complication such as diabetic ketoacidosis could appear. Also, adults with T2D may experience a hyperglycemic response to aerobic or resistance exercise, especially if they are insulin users. In those patients, excessive carbohydrate intake along with an exaggerated decrease in insulin can also induce hyperglycemia [81].

7. Conclusions

Physical exercise is an important part of the treatment of diabetes. It should be recommended and prescribed to all individuals with diabetes as part of management of glycemic control and overall health. Also, the prescription is important in population with prediabetes in order to prevent or delay the progress of T2D. Physical exercise practiced on a regular basis not only prevents diabetes, but also other cardiovascular risk factors. Specific recommendations and precautions will vary by the type of diabetes, age, type of exercise, and presence of diabetes-related health complications. Recommendations should be tailored to meet the specific needs of each individual. In addition, all adults should be encouraged to decrease the total amount of daily sedentary time and harmonizing sitting time with frequent sessions of activity. Finally, as a fundamental component, we must consider how to promote strategies aimed at behavioral changes to motivate the general population with and without diabetes to incorporate healthy changes in their lifestyle to improve their well-being.

8. References

1. World Health Organization. Physical Activity. [Internet] [Accessed in April 2021] Available in: https://www.who.int/health-topics/physical-activity#tab=tab_2

2. Colberg SR, Sigal RJ, Yardley JE, Riddell MC, Dunstan DW, Dempsey PC, Horton ES, Castorino K, Tate DF. Physical Activity/Exercise and Diabetes: A Position Statement of the American Diabetes Association. Diabetes Care, 2016; 39(11): 2065–79. https://doi.org/10.2337/dc16-1728

3. Bull FC, Al-Ansari SS, Biddle S, Borodulin K, Buman MP, Cardon G, et al. (2020). World Health Organization 2020 guidelines on physical activity and sedentary behaviour. Br J of Sports Med. 2020; 54(24): 1451–62. https://doi.org/10.1136/bjsports-2020-102955

4. Rydén L, Grant PJ, Anker SD, Berne C, Cosentino F, Danchin N et al. ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD: the Task Force on diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and developed in collaboration with the European Association for the Study of Diabetes (EASD). Eur Heart J. 2013; 34(39): 3035–87. https://doi.org/10.1093/eurheartj/eht108

5. International Diabetes Federation. IDF Diabetes Atlas. 9th edition, 2019. https://diabetesatlas.org/upload/resources/material/20200302_133351_IDFATLAS9e-final-web.pdf

6. Poretsky L. Principles of Diabetes Mellitus. Ed. Springer International Publishing; 2017

7. American Diabetes Association. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes—2021. Diabetes Care 2021; 44(Supplement 1): S15-S33. https://doi.org/10.2337/dc21-S002

8. Brugnara L, Murillo S, Novials A, Rojo-Martínez G, Soriguer F, Goday A, et al. Low Physical Activity and Its Association with Diabetes and Other Cardiovascular Risk Factors: A Nationwide, Population-Based Study. PloS one 2016; 11(8), e0160959. https://doi.org/10.1371/journal.pone.0160959

9. International Diabetes Federation. Type 1 diabetes. [Internet] [Accessed in April 2021] Available in: https://www.idf.org/aboutdiabetes/type-1-diabetes.html.

10. Exercise and NIDDM. Diabetes Care 1990; 13(7), 785–9. https://doi.org/10.2337/diacare.13.7.785

11. Coker RH, Kjaer M. Glucoregulation during exercise: the role of the neuroendocrine system. Sports medicine (Auckland, N.Z.) 2005; 35(7): 575–83. https://doi.org/10.2165/00007256-200535070-00003

12. Zinker BA, Lacy DB, Bracy D, Jacobs J, Wasserman DH. Regulation of glucose uptake and metabolism by working muscle. An in vivo analysis. Diabetes 1993; 42(7): 956–65. https://doi.org/10.2337/diab.42.7.956

13. Horowitz JF, Klein S. Lipid metabolism during endurance exercise. The American Journal of Clinical Nutrition 2000, 72(2 Suppl), 558S–63S. https://doi.org/10.1093/ajcn/72.2.558S

14. Hirsch IB, Marker JC, Smith LJ, Spina RJ, Parvin CA, Holloszy JO, Cryer PE. Insulin and glucagon in prevention of hypoglycemia during exercise in humans. The American Journal of Physiology 1991, 260(5 Pt 1), E695–E704. https://doi.org/10.1152/ajpendo.1991.260.5.E695

15. Sigal RJ, Fisher S, Halter JB, Vranic M, Marliss EB. The roles of catecholamines in glucoregulation in intense exercise as defined by the islet cell clamp technique. Diabetes 1996; 45(2): 148–56. https://doi.org/10.2337/diab.45.2.148

16. Thorell A, Hirshman MF, Nygren J, Jorfeldt L, Wojtaszewski JF, Dufresne SD, Horton ES, Ljungqvist O, Goodyear LJ. Exercise and insulin cause GLUT-4 translocation in human skeletal muscle. The American Journal of Physiology1999; 277(4):E733–41. https://doi.org/10.1152/ajpendo.1999.277.4.E733

17. Fujii N, Aschenbach WG, Musi N, Hirshman MF, Goodyear LJ. Regulation of glucose transport by the AMP-activated

protein kinase. The Proceedings of the Nutrition Society 2004; 63(2): 205–10. https://doi.org/10.1079/PNS2004340

18. Narkar VA, Downes M, Yu RT, Embler E, Wang YX, Banayo E, Mihaylova MM, Nelson MC, Zou Y, Juguilon H, Kang H, Shaw RJ, Evans RM. AMPK and PPARdelta agonists are exercise mimetics. Cell 2008; 134(3): 405–5. https://doi.org/10.1016/j.cell.2008.06.051

19. Goodyear LJ. The exercise pill--too good to be true?. The New England Journal of Medicine 2008; 359(17): 1842–4. https://doi.org/10.1056/NEJMcibr0806723

20. Pedersen BK, Fischer CP. Beneficial health effects of exercise-the role of IL-6 as a myokine. Trends in Pharmacological Sciences 2007; 28(4): 152–6. https://doi.org/10.1016/j.tips.2007.02.002

21. Pedersen BK, Febbraio MA. Muscles, exercise and obesity: skeletal muscle as a secretory organ. Nature reviews. Endocrinology 2012; 8(8): 457–65. https://doi.org/10.1038/nrendo.2012.49

22. Benatti FB, Pedersen BK. Exercise as an anti-inflammatory therapy for rheumatic diseases-myokine regulation. Nature reviews. Rheumatology. 2015; 11(2): 86–97. https://doi.org/10.1038/nrrheum.2014.193

23. Pedersen BK, Saltin B. Exercise as medicine - evidence for prescribing exercise as therapy in 26 different chronic diseases. Scandinavian Journal of Medicine & Science in Sports 2015; 25 Suppl 3, 1–72. https://doi.org/10.1111/sms.12581

24. Pedersen BK. Physical activity and muscle-brain crosstalk. Nature reviews. Endocrinology, 2019; 15(7): 383–92. https://doi.org/10.1038/s41574-019-0174-x

25. Severinsen M, Pedersen BK. Muscle-Organ Crosstalk: The Emerging Roles of Myokines. Endocrine Reviews 2020; 41(4): 594–609. https://doi.org/10.1210/endrev/bnaa016

26. Pedersen BK. Edward F. Adolph distinguished lecture: muscle as an endocrine organ: IL-6 and other myokines. Journal of applied physiology (Bethesda, Md: 1985) 2009; 107(4): 1006–14. https://doi.org/10.1152/japplphysiol.00734.2009

27. Karstoft K, Pedersen BK. Exercise and type 2 diabetes: focus on metabolism and inflammation. Immunology and Cell Biology 2016; 94(2): 146–50. https://doi.org/10.1038/icb.2015.101

28. Boström P, Wu J, Jedrychowski MP, Korde A, Ye L, Lo JC, Rasbach KA et al. A PGC1-α-dependent myokine that drives brown-fat-like development of white fat and thermogenesis. Nature 2012; 481(7382): 463–8. https://doi.org/10.1038/nature10777

29. Albrecht E, Norheim F, Thiede B, Holen T, Ohashi T, Schering L, et al. Irisin - a myth rather than an exercise-inducible myokine. Scientific Reports 2015; 5, 8889. https://doi.org/10.1038/srep08889

30. Jedrychowski MP, Wrann CD, Paulo JA, Gerber KK, Szpyt J, Robinson MM, Nair KS, Gygi SP, Spiegelman BM. Detection and Quantitation of Circulating Human Irisin by Tandem Mass Spectrometry. Cell Metabolism 2015; 22(4): 734–40. https://doi.org/10.1016/j.cmet.2015.08.001

26. Crane JD, MacNeil LG, Lally JS, Ford RJ, Bujak AL, Brar IK, Kemp BE, Raha S, Steinberg GR, Tarnopolsky MA. Exercise-stimulated interleukin-15 is controlled by AMPK and regulates skin metabolism and aging. Aging cell, 2015; 14(4): 625–634. https://doi.org/10.1111/acel.12341

27. Safdar A, Tarnopolsky MA. Exosomes as Mediators of the Systemic Adaptations to Endurance Exercise. Cold Spring Harbor perspectives in medicine 2018; 8(3), a029827. https://doi.org/10.1101/cshperspect.a029827

28. Frühbeis C, Helmig S, Tug S, Simon P, Krämer-Albers EM. Physical exercise induces rapid release of small extracellular vesicles into the circulation. Journal of Extracellular Vesicles 2015; 4, 28239. https://doi.org/10.3402/jev.v4.28239

29. Safdar A, Saleem A, Tarnopolsky MA. The potential of endurance exercise-derived exosomes to treat metabolic

diseases. Nature Reviews. Endocrinology 2016; 12(9): 504–17. https://doi.org/10.1038/nrendo.2016.76

30. Castaño C, Mirasierra M, Vallejo M, Novials A, Párrizas M. Delivery of muscle-derived exosomal miRNAs induced by HIIT improves insulin sensitivity through down-regulation of hepatic FoxO1 in mice. Proceedings of the National Academy of Sciences of the United States of America 2020; 117(48): 30335–43. https://doi.org/10.1073/pnas.2016112117

31. Riddell MC, Gallen IW, Smart CE, Taplin CE, Adolfsson P, Lumb AN, et al. (2017). Exercise management in type 1 diabetes: a consensus statement. The Lancet. Diabetes & Endocrinology 2017; 5(5): 377–90. https://doi.org/10.1016/S2213-8587(17)30014-1

32. American Diabetes Association. Prevention or Delay of Type 2 Diabetes: Standards of Medical Care in Diabetes-2021. Diabetes Care. 2021;44 (Suppl 1):S34-S39. https://doi.org/10.2337/dc21-S003

33. Wing RR. Physical activity in the treatment of the adulthood overweight and obesity: current evidence and research issues. Medicine and Science in Sports and Exercise 1999, 31(11 Suppl), S547–52. https://doi.org/10.1097/00005768-199911001-00010

34. Snowling NJ, Hopkins WG. Effects of different modes of exercise training on glucose control and risk factors for complications in type 2 diabetic patients: a meta-analysis. Diabetes Care 2006; 29(11): 2518–27. https://doi.org/10.2337/dc06-1317

35. Chen L, Pei JH, Kuang J, Chen HM, Chen Z, Li ZW, Yang HZ. Effect of lifestyle intervention in patients with type 2 diabetes: a meta-analysis. Metabolism: Clinical and Experimental 2015; 64(2): 338–47. https://doi.org/10.1016/j.metabol.2014.10.018

36. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, Nathan DM, & Diabetes Prevention Program Research Group Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. The New England Journal of Medicine 2002; 346(6): 393–403. https://doi.org/10.1056/NEJMoa012512

37. Tuomilehto J, Lindström J, Eriksson JG, Valle TT, Hämäläinen H, Ilanne-Parikka P, … & Finnish Diabetes Prevention Study Group. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. The New England Journal of Medicine 2001; 344(18): 1343–50. https://doi.org/10.1056/NEJM200105033441801

38. Li G, Zhang P, Wang J, Gregg EW, Yang W, Gong Q, et al. The long-term effect of lifestyle interventions to prevent diabetes in the China Da Qing Diabetes Prevention Study: a 20-year follow-up study. Lancet (London, England) 2008; 371(9626): 1783–89. https://doi.org/10.1016/S0140-6736(08)60766-7

39. Saito T, Watanabe M, Nishida J, Izumi T, Omura M, Takagi T, … & Zensharen Study for Prevention of Lifestyle Diseases Group. Lifestyle modification and prevention of type 2 diabetes in overweight Japanese with impaired fasting glucose levels: a randomized controlled trial. Archives of Internal Medicine 2011; 171(15): 1352–60. https://doi.org/10.1001/archinternmed.2011.275

40. Russo LM, Nobles C, Ertel KA, Chasan-Taber L, Whitcomb BW. Physical activity interventions in pregnancy and risk of gestational diabetes mellitus: a systematic review and meta-analysis. Obstetrics and Gynecology 2015; 125(3): 576–582. https://doi.org/10.1097/AOG.0000000000000691

41. Sanabria-Martínez G, García-Hermoso A, Poyatos-León R, Álvarez-Bueno C, Sánchez-López M, Martínez-Vizcaíno V. Effectiveness of physical activity interventions on preventing gestational diabetes mellitus and excessive maternal weight gain: a meta-analysis. BJOG: an International Journal of Obstetrics and Gynaecology; 122(9): 1167–74. https://doi.org/10.1111/1471-0528.13429

42. Qiu S, Cai X, Schumann U, Velders M, Sun Z, Steinacker JM. Impact of walking on glycemic control and other cardiovascular risk factors in type 2 diabetes: a meta-analysis. PloS One 2014; 9(10), e109767. https://doi.org/10.1371/journal.pone.0109767

43. Chudyk A, Petrella RJ. Effects of exercise on cardiovascular risk factors in type 2 diabetes: a meta-analysis. Diabetes Care 2011; 34(5), 1228–37. https://doi.org/10.2337/dc10-1881

44. Thomas DE, Elliott EJ, Naughton GA. Exercise for type 2 diabetes mellitus. The Cochrane Database of Systematic Reviews 2006; (3), CD002968. https://doi.org/10.1002/14651858.CD002968.pub2

45. Umpierre D, Ribeiro PA, Kramer CK, Leitão CB, Zucatti AT, Azevedo MJ, Gross JL, Ribeiro JP, Schaan BD. Physical activity advice only or structured exercise training and association with HbA1c levels in type 2 diabetes: a systematic review and meta-analysis. JAMA 2011; 305(17): 1790–99. https://doi.org/10.1001/jama.2011.576

46. Liubaoerjijin Y, Terada T, Fletcher K, Boulé NG. Effect of aerobic exercise intensity on glycemic control in type 2 diabetes: a meta-analysis of head-to-head randomized trials. Acta Diabetologica 2016; 53(5): 769–81. https://doi.org/10.1007/s00592-016-0870-0

47. Bohn B, Herbst A, Pfeifer M, Krakow D, Zimny S, Kopp F, Melmer A, Steinacker JM, Holl RW, DPV Initiative. Impact of Physical Activity on Glycemic Control and Prevalence of Cardiovascular Risk Factors in Adults With Type 1 Diabetes: A Cross-sectional Multicenter Study of 18,028 Patients. Diabetes Care 2015; 38(8): 1536–43. https://doi.org/10.2337/dc15-0030

48. Wu N, Bredin S, Guan Y, Dickinson, K., Kim, D. D., Chua, Z., Kaufman, K., & Warburton, D. (2019). Cardiovascular Health Benefits of Exercise Training in Persons Living with Type 1 Diabetes: A Systematic Review and Meta-Analysis. Journal of clinical medicine, 8(2), 253. https://doi.org/10.3390/jcm8020253

49. American Diabetes Association. Cardiovascular Disease and Risk Management: Standards of Medical Care in Diabetes—2021. Diabetes Care 2021; 44 (Supplement 1): S125-S150. https://doi.org/10.2337/dc21-S010

50. Lind M, Svensson AM, Kosiborod M, Gudbjörnsdottir S, Pivodic A, Wedel H, Dahlqvist S, Clements M, Rosengren A. Glycemic control and excess mortality in type 1 diabetes. The New England Journal of Medicine 2014; 371(21): 1972–82. https://doi.org/10.1056/NEJMoa1408214

51. Rawshani A, Rawshani A, Franzén S, Eliasson B, Svensson AM, Miftaraj M, McGuire DK, Sattar N, Rosengren A, Gudbjörnsdottir S. Mortality and Cardiovascular Disease in Type 1 and Type 2 Diabetes. The New England Journal of Medicine 2017; 376(15), 1407–18. https://doi.org/10.1056/NEJMoa1608664

52. Liu G, Li Y, Hu Y, Zong G, Li S, Rimm EB, Hu FB, Manson JE, Rexrode KM, Shin HJ, Sun Q. Influence of Lifestyle on Incident Cardiovascular Disease and Mortality in Patients With Diabetes Mellitus. Journal of the American College of Cardiology 2018; 71(25): 2867–76. https://doi.org/10.1016/j.jacc.2018.04.027

53. Gong Q, Zhang P, Wang J, Ma J, An Y, Chen, Y,… & Da Qing Diabetes Prevention Study Group. Morbidity and mortality after lifestyle intervention for people with impaired glucose tolerance: 30-year results of the Da Qing Diabetes Prevention Outcome Study. The Lancet. Diabetes & Endocrinology 2019; 7(6): 452–61. https://doi.org/10.1016/S2213-8587(19)30093-2

54. Look AHEAD Research Group, Wing RR, Bolin P, Brancati FL, Bray GA, Clark JM, Coday M, el al. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. The New England Journal of Medicine 2013; 369(2): 145–54. https://doi.org/10.1056/NEJMoa1212914

55. Look AHEAD Research Group, Gregg EW, Jakicic JM, Blackburn G, Bloomquist P, Bray GA, Clark JM et al. Association of the magnitude of weight loss and changes in physical fitness with long-term cardiovascular disease outcomes in overweight or obese people with type 2 diabetes: a post-hoc analysis of the Look AHEAD randomised clinical trial. The Lancet. Diabetes & Endocrinology 2016; 4(11): 913–21. https://doi.org/10.1016/S2213-8587(16)30162-0

56. Tikkanen-Dolenc H, Wadén J, Forsblom C, Harjutsalo V, Thorn LM, Saraheimo M, ..., & FinnDiane Study Group (2017). Frequent and intensive physical activity reduces risk of cardiovascular events in type 1 diabetes. Diabetologia 2017; 60(3): 574–580. https://doi.org/10.1007/s00125-016-4189-8

57. Tielemans SM, Soedamah-Muthu SS, De Neve M, Toeller M, Chaturvedi N, Fuller JH, Stamatakis E. (2013). Association of physical activity with all-cause mortality and incident and prevalent cardiovascular disease among patients with type 1 diabetes: the EURODIAB Prospective Complications Study. Diabetologia 2013; 56(1): 82–91. https://doi.org/10.1007/s00125-012-2743-6

58. Pongrac Barlovic D, Tikkanen-Dolenc H, Groop PH. Physical Activity in the Prevention of Development and Progression of Kidney Disease in Type 1 Diabetes. Current Diabetes Reports 2019; 19(7): 41. https://doi.org/10.1007/s11892-019-1157-y

59. Cai Z, Yang Y, Zhang J. Effects of physical activity on the progression of diabetic nephropathy: a meta-analysis. Bioscience Reports 2021; 41(1), BSR20203624. https://doi.org/10.1042/BSR20203624

60. Tikkanen-Dolenc H, Wadén J, Forsblom C, Harjutsalo V, Thorn LM, Saraheimo M, Elonen N, Tikkanen HO, Groop PH, FinnDiane Study Group (2017). Physical Activity Reduces Risk of Premature Mortality in Patients With Type 1 Diabetes With and Without Kidney Disease. Diabetes Care 2017; 40(12): 1727–32. https://doi.org/10.2337/dc17-0615

61. Tikkanen-Dolenc H, Wadén J, Forsblom C, Harjutsalo V, Thorn LM, Saraheimo M, …, FinnDiane Study Group. Frequent physical activity is associated with reduced risk of severe diabetic retinopathy in type 1 diabetes. Acta Diabetologica 2020; 57(5): 527–34. https://doi.org/10.1007/s00592-019-01454-y

62. Powers S and Howley ET. Exercise physiology: theory and application to fitness and performance. 9th edition. Ed. McGraw-Hill Education; 2014

63. Hamman RF, Wing RR, Edelstein SL, Lachin JM, Bray GA, Delahanty L, et al. Effect of weight loss with lifestyle intervention on risk of diabetes. Diabetes Care 2006; 29(9):2102–07. https://doi.org/10.2337/dc06-0560

64. American Diabetes Association. Facilitating Behavior Change and Well-being to Improve Health Outcomes: Standards of Medical Care in Diabetes—2021 Diabetes Care 2021; 44(Supplement 1): S53-S72. https://doi.org/10.2337/dc21-S005

65. Scott SN, Cocks M, Andrews RC, Narendran P, Purewal TS, Cuthbertson DJ, Wagenmakers A, Shepherd SO. High-Intensity Interval Training Improves Aerobic Capacity Without a Detrimental Decline in Blood Glucose in People With Type 1 Diabetes. The Journal of Clinical Endocrinology and Metabolism 2019; 104(2): 604–612. https://doi.org/10.1210/jc.2018-01309

66. Bax JJ, Young LH, Frye RL, Bonow RO, Steinberg HO, Barrett EJ. Screening for Coronary Artery Disease in Patients With Diabetes. Diabetes Care 2007; 30(10): 2729-36. https://doi.org/10.2337/dc07-9927

67. Young LH, Wackers FJ, Chyun DA, Davey JA, Barrett EJ, Taillefer R, …., & DIAD Investigators. Cardiac outcomes after screening for asymptomatic coronary artery disease in patients with type 2 diabetes: the DIAD study: a randomized controlled trial. JAMA 2009; 301(15): 1547–55. https://doi.org/10.1001/jama.2009.476

68. Colberg SR. Exercise and Diabetes: A Clinician's Guide to Prescribing Physical Activity. 1st ed. Alexandria, VA, American Diabetes Association; 2013.

69. Smith AG, Russell J, Feldman EL, Goldstein J, Peltier A, Smith S, et al. Lifestyle intervention for pre-diabetic neuropathy. Diabetes Care 2006; 29(6): 1294–99. https://doi.org/10.2337/dc06-0224

70. Spallone V, Ziegler D, Freeman R, Bernardi L, Frontoni S, Pop-Busui R,…, & Toronto Consensus Panel on Diabetic Neuropathy. Cardiovascular autonomic neuropathy in diabetes: clinical impact, assessment, diagnosis, and management. Diabetes/Metabolism Research and Reviews 2011; 27(7): 639–53. https://doi.org/10.1002/dmrr.1239

71. Pop-Busui R, Evans GW, Gerstein HC, Fonseca V, Fleg JL, Hoogwerf BJ, …, & Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of cardiac autonomic dysfunction on mortality risk in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. Diabetes Care 2010; 33(7): 1578–84. https://doi.org/10.2337/dc10-0125

72. Peters A, Laffel L, Colberg SR, Riddell MC. Physical activity: regulation of glucose metabolism, clinical management strategies, and weight control. In American Diabetes Association/JDRF Type 1 Diabetes Sourcebook. Alexandria, VA, American Diabetes Association; 2013

73. Frier BM. Hypoglycaemia in diabetes mellitus: epidemiology and clinical implications. Nature Reviews.

Endocrinology 2014; 10(12): 711–22. https://doi.org/10.1038/nrendo.2014.170

74. Burke LM, Collier GR, Hargreaves M. Muscle glycogen storage after prolonged exercise: effect of the glycemic index of carbohydrate feedings. Journal of Applied Physiology (Bethesda, Md: 1985) 1993; 75(2): 1019–23. https://doi.org/10.1152/jappl.1993.75.2.1019

75. Brazeau AS, Rabasa-Lhoret R, Strychar I, Mircescu H. Barriers to physical activity among patients with type 1 diabetes. Diabetes Care 2008; 31(11): 2108–09. https://doi.org/10.2337/dc08-0720

76. Novials A, Murillo S. Adapting the Consumption of Carbohydrates for Diabetic Athletes. In: Chuang-Fa Chang. Carbohydrates: Comprehensive Studies on Glycobiology and Glycotechnology ed InTechOpen; 2012. http://dx.doi.org/10.5772/51570 2012 p356-370

77. Campbell MD, Walker M, Bracken RM, Turner D, Stevenson EJ, Gonzalez, JT, Shaw JA, West DJ. Insulin therapy and dietary adjustments to normalize glycemia and prevent nocturnal hypoglycemia after evening exercise in type 1 diabetes: a randomized controlled trial. BMJ Open Diabetes Research & Care 2015; 3(1), e000085. https://doi.org/10.1136/bmjdrc-2015-000085

78. Marliss EB, Vranic M. Intense exercise has unique effects on both insulin release and its roles in glucoregulation: implications for diabetes. Diabetes 2002; 51 Suppl 1, S271–S283. https://doi.org/10.2337/diabetes.51.2007.s271

79. Fahey AJ, Paramalingam N, Davey RJ, Davis EA, Jones TW, Fournier PA. (2012). The effect of a short sprint on postexercise whole-body glucose production and utilization rates in individuals with type 1 diabetes mellitus. The Journal of Clinical Endocrinology and Metabolism 2012; 97(11): 4193–4200. https://doi.org/10.1210/jc.2012-1604

80. Turner D, Luzio S, Gray BJ, Bain SC, Hanley S, Richards A, Rhydderch DC, Martin R, Campbell MD, Kilduff LP, West DJ, Bracken RM. Algorithm that delivers an individualized rapid-acting insulin dose after morning resistance exercise counters post-exercise hyperglycaemia in people with Type 1 diabetes. Diabetic Medicine: a Journal of the British Diabetic Association, 2016; 33(4): 506–10. https://doi.org/10.1111/dme.12870

81. Gordon BA, Bird SR, MacIsaac RJ, Benson AC. Does a single bout of resistance or aerobic exercise after insulin dose reduction modulate glycaemic control in type 2 diabetes? A randomised cross-over trial. Journal of Science and Medicine in Sport 2016; 19(10): 795–99. https://doi.org/10.1016/j.jsams.2016.01.004