- Review Article -

Why should people with type 1 diabetes exercise regularly?

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Abstract

Plethoric evidence reminds of the protective effects of exercise against a number of health risks, across all ages, in the general population. The benefits of exercise for individuals with type 2 diabetes are indisputable. An in-depth understanding of energy metabolism has reasonably entailed exercise as a cornerstone in the lifestyle of almost all subjects with type 1 diabetes. Nevertheless, individuals with type 1 diabetes often fail in accomplishing exercise guidelines and they are less active than their peer without diabetes. Two major obstacles are feared by people with type 1 diabetes who wish to exercise regularly: management of blood glucose control and hypoglycemia. Nowadays strategies, including glucose-monitoring technology and insulin pump therapy, have significantly contributed to the participation in regular physical activity, and even in competitive sports, for people with type 1 diabetes. Novel modalities of training, like different-intensity, interspersed exercise, are as well promising.

The beneficial potential of exercise in type 1 diabetes is multi-faceted and it has to be fully exploited because it goes beyond the insulin-mimetic action, possibly through immunomodulation.

Keywords:

Glucose monitoring, Insulin pump, Autoimmunity, Hypoglycemia, Immunomodulation

Abbreviations:

CGM, continuous glucose monitoring; CSII, continuous subcutaneous insulin infusion; CVD, cardiovascular disease; GLP-1, glucagon-like peptide-1; IL-6, interleukin 6; IMCL, intramyocellular lipid content; IT, islet transplantation; MDII, multiple daily insulin injections; NEFA, non-esterified fatty acid; SMBG, self-monitoring blood glucose; T1D, type 1 diabetes.

1. From type 2 to type 1 exercise-recommendations: over the guidelines

In 1993, Kahn et al. first described the hyperbolic relationship between β-cell function and insulin sensitivity [1]. Physical exercise enables the achievement of better positions on the glucose-tolerance curve by ameliorating insulin sensitivity in any subject, either with type 2 (T2D) or type 1 diabetes (T1D). Traditionally, physical exercise is promoted in T2D where insulin action is deficient in the context of insulin resistance and/or inappropriate insulin secretion. However, even in T1D, in the dysregulation of immune system function, β-cell toxicity is mediated by a complex interplay between oxidative stress and inflammation, for which exercise could be protective. Recent studies have suggested that physical exercise may interfere with immune system function even at low intensity and duration.

Although current guidelines are robust and straightforward in recommending doses of exercise (types, duration, intensity) for subjects with T2D, a complex and multifactorial strategy has been outlined for the exercise-recommendations in T1D with a large and uncertain therapeutic range of efficacy (due to difficult glycemic control, and adherence). This advocates for a personalized, omni-comprehensive approach to fully exploit the exercise-benefits in people with T1D.

1.1 Immunomodulatory indications from animal and human models

The nonobese diabetic (NOD) mouse has been studied as the elective model to mimic the diabetes progression in humans as it is characterized by progressive autoimmune destruction of pancreatic β-cells. We underwent NOD mice to a 12-week program of moderate-intensity treadmill training

to investigate immunological and inflammatory modifications during T1D progression [2]. We ascertained glucose-lowering effects induced by exercise in the late states of diabetes, whereas control untrained NOD mice revealed the presence of larger infiltrates at the end of the study. These results suggested that exercise may exert a positive immunomodulation of systemic functions to both T1D and inflammation.

Within a unifying continuum of diabetes, we gathered a putative immunomodulatory effect of exercise in patients with T1D. According to our epidemiological screening, physical exercise would be able to prolong the "honeymoon", i.e. the period of time, in early pathogenesis of T1D, characterized by reduced need for exogenous insulin. We have seen honeymoon to be definitively longer in active people, like athletes with T1D. Specifically, we found a putative inverse relationship between autoimmunity markers (GAD, IA) and exercise-derived energy expenditure [3, 4].

In other longitudinal studies (observational and intervention) we showed that exercise may positively modulate immune system function in β-cells transplanted recipients. Active subjects with T1D, following islet transplantation (IT), exhibited ameliorated scores of disease management, quality of life [5], metabolic control, body composition [6]. In addition, in IT subjects, physical exercise was capable to counteract diabetic symptoms and mitigated the side effects of immunosuppressive drugs and graft dysfunction [7, 8]. After IT, in fact, progressive insulin resistance might arise as a result of immunosuppression and chronic inflammation.

Literature reports several data supporting a complex interplay between immunological and metabolic scenarios. Fischer et al. demonstrated the involvement of interleukin-6 (IL-6) in the modulation of the immunological and metabolic responses to high-intensity exercise [9]. Ellingsgaard et al. documented positive effects of IL-6 on glucagon- [10] and insulin secretion through the action on glucagon-like peptide-1 (GLP-1) secretion, release, and subsequent β-cell signaling [11]. Da Silva Krause et al. confirmed that IL-6 promotes insulin secretion from clonal β-cells and pancreatic islets as this cytokine may exert GLP1-independent effects in the islet *in vivo* [12]. Suzuki et al. suggested IL-6 acts directly on pancreatic β-cells [13]. Altogether these IL-6 exercise-induced effects may restore the imbalance in the Th1/Th2 cytokines ratio observed in T1D, protecting from the autoimmune process directed to β-cells. We hypothesize that a direct exercise-intervention study would be capable to gain a greater effect on the immunological stand-point, as shown in previous studies.

2. Exercise in T1D: the risk-benefit analysis

Physical activity, sports and exercise should be encouraged in people with T1D for similar reasons it should be encouraged in people with T2D, or in the general population. Overall, regular exercise can decrease risk factors for cardiovascular diseases (CVD), it offers protection against all-cause mortality [4] and it may even improve quality of life in many individuals, under a variety of conditions [14]. Likewise for individuals with T2D, physical activity should be embodied in the management of T1D as it increases insulin sensitivity (both short and long term), lowers blood glucose levels, reduces body fat (and ameliorates body mass

composition [6]), improves cardiovascular function. However, due to the loss of the β-cell pancreatic mass and/or -function, subjects with T1D uniquely face a number of challenges in preparation for, during, and after each session of exercise. While the metabolic control is typically achievable in T2D as adaptive response to exercise, a successful management of blood glucose is instead uncertain in T1D. If insulin levels are excessive, hypoglycemia may arise during and after exercise. On the contrary, if insulin levels are deficient, exercise may lead to hyperglycemia or ketosis. Appropriate approaches, combining adjusted insulin therapy and diet, may accommodate daily exercise. However, an individualized risk-benefit analysis must be run when prescribing an exercise program for people with T1D.

Strategies should be developed to minimize the risk of hypoglycemia – the most frequent event during/after exercise, given the derangements in fuel metabolism of individuals with T1D. Research in the area of exercise and diabetes has shown the importance of tight glucose control as a pillar in the management of T1D, especially under physical activity stimulation. Relevant precautions may include reduced doses of insulin in anticipation of exercise [15]; ingestion of readily absorbable carbohydrates [16]; adjustment of basal insulin infusion in pump therapy [17] (Figure 1). In fact, the insulin pump therapy, allowing a continuous subcutaneous insulin infusion (CSII), represents one of the most cost-effective approaches in different populations with T1D. Integrated monitoring systems, comprising CSII and continuous glucose monitoring (CGM), have been proved to be efficient in exploiting the beneficial effects of exercise within a comprehensive T1D-based educational approach.

3. Abnormal endocrine responses to exercise in T1D

In healthy metabolism, glucose homeostasis is ensured during exercise through an array of neuroendocrine responses involving the growth hormone, cortisol, insulin, glucagon, and epinephrine. In other words, these responses modulate the balancing between glucose production and glucose utilization, during exercise, in order to maintain euglycemia (Figure 2). Unfortunately, these counter-regulatory responses may be abnormal or lost in T1D, and hypoglycemia arises as a frequent event among T1D-metabolic complications. In the early phase of the disease, usually before the onset of autonomic neuropathy, the sympathoadrenal responses are adequate to counteract hypoglycemia. However this defense can also be attenuated in later stages of T1D, and the consequent derangements, combined together, further increase the likelihood of hypoglycemia (hence, "hypoglycemia begets hypoglycemia"). Frequent hypoglycemia has been shown to reduce the glycemic threshold for activation of the counter-regulatory response needed to restore euglycemia during a subsequent hypoglycemic episode. As a result, some individuals develop hypoglycemia-associated autonomic failure (HAAF) and do not experience and respond to the potentially life-saving warning symptoms, therefore they are at increased risk of seizures, coma and death [18, 19]. Nevertheless, some recent studies found that in T1D, exercise and hypoglycemia may have mutual blunting effect to their counter-regulatory responses [20, 21].

To summarize, blood glucose response to exercise is determined by a balance between hepatic glucose output and muscle glucose uptake; this balance is a function of diet, therapy, parameters related to exercise modality, and characteristics of the subjects.

3.1 Exercise metabolism in health

During exercise, due to the increased metabolism, blood glucose is rapidly exhausted . However, there are physiological mechanisms helping to maintain euglycemic levels. Key metabolic pathways interact to regulate the rate of glucose metabolism and to direct cellular bioenergetics toward a defined homeostasis. These mechanisms include:

1. Mobilization of glucose from liver glycogen stores;
2. Mobilization of non-esterified fatty acid (NEFA) from adipose tissue (which spares blood glucose);
3. Gluconeogenesis from the non-carbohydrate precursor such as amino acids, lactic acid, and glycerol;
4. Blocking the entry of glucose into cells and forcing the cells to use NEFA as a fuel.

3.2 Exercise dys-metabolism in T1D

Glycolysis - Pyruvate and lactate concentration. Intense short-term exercise induces glycogen breakdown to provide the substrate for activating anaerobic glycolysis and to assure constant energy supply. However, the process results in accumulation of plasma pyruvate and lactate. Many studies have confirmed an increased concentration of serum lactate and pyruvate after exercise. Unfortunately, in T1D the pyruvate response is found to be blunted [22]. Given that insulin inhibits glycogen breakdown, the presence of increased insulin levels in T1D may result in a reduced glycogenolytic response [23].

Fat metabolism. During exercise, when the energy supply does not match the demand, a low plasma glucose level can occur. As a result, catecholamines are released to stimulate lipolysis. This process, which involves reduction of

triglycerides to free fatty acids, is catalyzed by lipase, and it is activated through the action of cortisol, epinephrine, norepinephrine, and growth hormone (GH). In response to exercise, healthy individuals show an increase in levels of free fatty acids and glycerol, as end-products of lipolysis [22, 24]. In T1D individuals, exercise-induced lipolysis is attenuated, again attributable to high insulin levels [23].

Protein metabolism. During exercise, when glucose is not available as the primary fuel, protein breakdown serves to provide an alternative source of energy. Studies indicate that high circulating insulin level in T1D may attenuate the process of protein breakdown. This is evidenced by lower levels of leucine, a product of protein breakdown [23].

Insulin response. Serum insulin levels in T1D patients are found to be high after 30 minutes of exercise. This increase in insulin could be one of the reasons for the diminished endocrine- and metabolic response to exercise in T1D [23]. Earlier, a study conducted to understand the exercise-induced lipolysis found increased levels of liposoluble vitamins in the blood stream, released from the subcutaneous fat tissue [24, 25]. This observation implies that the insulin stored in the subcutaneous tissue may be gradually released in response to exercise due to lipolysis. High levels of insulin may reach supra-physiological levels, leading to insulin resistance in T1D [26, 27]. In addition, studies have also found impaired glucose utilization and impaired insulin-induced NEFA suppression in T1D [28, 29]. Insulin resistance is also evidenced in hepatic and skeletal muscle tissue, despite good glycemic control in T1D [30]. A study conducted on T1D adolescents revealed impaired functional exercise capacity and decreased insulin sensitivity [31]. However, these individuals had paradoxically normal

intramyocellular lipid content (IMCL) which challenges the previous finding that IMCL accumulation a marker for insulin resistance in both T1D and T2D [32, 33].

3.3 Hypoglycemia and delayed glucose recovery

T1D patients are at high risk of hypoglycemia following exercise; in addition, there is delayed glucose recovery from hypoglycemia attributable to blunted glucagon response, reduced adrenomedullary response, and diminished clearance of injected insulin. In healthy people, the pancreas secretes glucagon in response to hypoglycemia. Glucagon stimulates the breakdown of glycogen in the liver (hepatic glycogenolysis). As a result, the glycogen is converted to glucose, thereby normalizing plasma glucose levels. Many studies have proved the fact that plasma glucagon response to hypoglycemia is markedly attenuated in diabetes. In long-standing T1D, this glucagon response is irreversibly lost [34, 35]. As a result, the body relies on other counterregulatory responses and takes a longer time to normalize the hypoglycemia induced by exercise.

Hypoglycemia is a potent stimulator of epinephrine. In response to hypoglycemia, the adrenal medulla secretes epinephrine which helps to counterregulate low glucose levels by promoting glycogenolysis and lipolysis. However, it has been found that in T1D patients, the plasma epinephrine levels are one third of their healthy counterparts, implying a blunted adrenomedullary response [36].

A very crucial factor in glucose recovery from hypoglycemia is the clearance of injected insulin. Research indicates that T1D patients have diminished clearance of injected insulin as evidenced by the prolonged initial half-time of disappearance of injected insulin [36]. It implies that T1D patients develop insulin resistance over time, which interferes with glucose uptake and their

utilization by the tissues. Another important consideration is the body's dependability on the type of counterregulatory response to hypoglycemia. Studies have reported that recovery from insulin-induced hypoglycemia is unaffected by adrenergic blockade in healthy controls [37]. It indicates that adrenomedullary response (epinephrine secretion) is not critical to glucose recovery from hypoglycemia unless glucagon response is absent or reduced [34, 37]. It implies that T1D patients, with blunted or absent glucagon response, are dependent on epinephrine-mediated response for glucose recovery from hypoglycemia. This has been confirmed in studies that showed lower mean blood glucose levels, with smaller increments in mean plasma glucagon, in T1D patients when compared to their healthy counterparts [38, 39].

Exercise-induced hypoglycemia. In healthy people, the insulin levels drop during exercise, which stimulates the secretion of glucagon and promotes glycogenolysis. In T1D, the exogenous insulin levels do not drop, increasing the risk of exercise-induced hypoglycemia [39–41].

There could be several possible reasons for the body's inability to reduce insulin levels. Firstly, the exercise is usually performed in a 0–4-h period following an insulin injection. As a result, the insulin levels might not decrease due to the inadequate timeframe, and, furthermore, due to the pharmacokinetics of the insulin and time of its peak action [15]. Secondly, the injected insulin may get absorbed rapidly form the subcutaneous tissue, following exercise, resulting in increased insulin levels [42]. The increased levels of insulin promote peripheral uptake and utilization of glucose, aggravating the hypoglycemic state, complicated by limited glucagon response [43]. Thirdly, T1D patients have an attenuated glucagon response to hypoglycemia, decreasing the glycogen

breakdown to glucose, which would have countered the hypoglycemia in healthy individuals [37, 38, 44].

In some people with T1D, the glucagon response to exercise may be intact, in absence of hypoglycemia [44]. However, the glucagon response may be blunted if previously exposed to hypoglycemia [21]. Exercise-induced hypoglycemia may also be a result of blunted adrenomedullary responses to exercise in T1D [21]. T1D patients with poor glycemic control may have low hepatic glycogen content [45], again contributing to exercise-induced hypoglycemia.

Late glycemic excursions. Many patients with T1D experience exercise-induced late-onset hypoglycemia [18], about 7-11 hours post-exercise ("lag effect" of exercise) [46, 47]. This might be harmful, especially because unaware: patients may unconsciously experience hypoglycemia during sleep. Physical activity during the daytime accelerate the risk of nocturnal hypoglycemia to about 30–40% [48–52]. This incidence resembles the need to accurately evaluate and identify the relative metabolic alterations occurring inside the body. Insulin sensitivity is pronounced in T1D immediately after exercise and again 7–11 hours later, increasing the risk for late glycemic excursions [46]. This implies the mandatory modification in the insulin therapy post exercise, especially the bedtime insulin [48].

3.4 Exercise-induced hyperglycemia

Decreased insulin levels in the portal circulation can result in hyperglycemia. In the absence of insulin, the muscle cells do not utilize glucose as fuel, and instead rely on fatty acids and ketones, leading to ketoacidosis. If the glycogenolysis from liver continues, without the muscles taking up glucose, the plasma glucose

levels can shoot up, resulting in hyperglycemia [53]. Hyperglycemia can ensue following high-intensity exercise that increases cathecolamine and cortisol levels [54], augmenting, in turn, hepatic glucose production and limiting peripheral glucose disposal. In healthy individuals this increase in cathecolamines is compensated by for enhanced insulin secretion upon termination of exercise, whereas in T1D subjects such a phenomenon might exacerbate post-exercise hyperglycemia. However this hyperglycemic effect is transitory in diabetic subjects, lasting 1-2 hours in the recovery time [55, 56].

Obviously, if a patient has hyperglycemia and presence of urinary ketones, exercise should be delayed [57, 58]. Vigorous activity should be avoided especially with known insulin omission. Conversely, if elevated blood glucose is clearly attributable to underdosing insulin at the preceding meal, exercise may not be postponed based solely on hyperglycemia.

3.5 Exercise types

The physiological response to exercise depends upon the intensity, volume and frequency of exercises along with the muscle group involved. The rate of glycogen depletion is directly proportional to the intensity of exercise. Glycogenolysis is rapid during high-intensity exercise. The process of glycogen breakdown is regulated by epinephrine levels. High-intensity exercise increases plasma epinephrine levels which in turn increase glycogen breakdown.

Some exercise types, such as aerobic exercise, even if performed for only 15 min, cause a significant increase in plasma GH levels. The peak values are found at the end of the activity [59]. Other factors influencing the GH response to exercise include physical fitness, gender and age [59]. Studies show a linear dose–

response between exercise intensity and GH secretion [60, 61]. Research studies have also found that sustained endurance training blunts the acute exercise-induced GH release [62].

Anaerobic exercise involves intense muscular contraction resulting in accumulation of lactic acid. High lactate levels reduce the uptake and utilization of plasma glucose and NEFA in the skeletal muscle. It also promotes hepatic glucose production. These two mechanisms combined may result in hyperglycemia in T1D [63–65]. However, studies show that a 10-s high-intensity anaerobic sprint may help prevent early post-exercise hypoglycemia in T1D [66, 67]. Weight training before the onset of aerobic exercise has also been found to be helpful in maintaining the blood glucose levels in T1D [68].

As previously reported, intense aerobic exercise combined with equally intense anaerobic activity may increase blood glucose levels for 1–2 h in recovery [55, 56].

3.5.1 High Intensity Intermittent Training: a possible new frontier of glucose control in T1D?

Intermittent high intensity exercise is a fascinating modality of training that consists in moderate intensity exercise with short bouts – repetitive sprinting – of interspersed all-out efforts. Few randomized controlled trials have investigated the beneficial effects of vigorous intensity exercise, specifically high intensity intermittent training, in adults with T1D. As mentioned, a single all-out sprint of 10 s, upon completion of exercise, may counter the drop in glucose occurring post-exercise by activation of GLUT4. Conversely, the same 10 s burst executed before exercise did not impede the hypoglycemic event, although a stabilization of glycemic levels was achieved post-exercise. In fact, intermittent high-intensity

exercise should be preferred over continuous moderate-intensity aerobic exercise to help prevent extreme excursion of glucose levels [69, 70]. Furthermore, intermittent high-intensity exercise decreases glucose disposal compared with continuous moderate intensity exercise, implying a high flexibility of the former type of exercise in shifting fuel metabolism towards consumption of alternatives substrates [71]. To conclude, intermittent high intensity exercise reduces metabolic destabilization post-effort; it offers protection against nocturnal hypoglycemia in athletes with T1D [70], and it has been also accompanied with enhanced muscle oxidative metabolism in young subjects with T1D [64]. International guidelines recommend to have participated at least in regular moderate-intensity exercise before performing short bursts of very intense activity interspersed with short period of recovery. Evidence for the efficacy of this training in obtaining stable glycemic control is lacking, however the optimal high-intensity intermittent training protocol has yet to be fully tested and determined.

4. How to maximize exercise benefits in T1D

Over the past decades a wide spectrum of scientific advances have been spanned through the diabetes management in order to greatly improve the psychological and behavioral burden of these patients. Options offered by technology and clinical care are various, ranging from frequent self-monitoring of blood glucose (SMBG) to islet-transplantation (IT). Use of blood glucose monitors is pivotal for controlling glycemic excursions in response to exercise: insulin and carbohydrate intake can be accordingly adjusted to prevent dysglycemic events (hyper-, or more often, hypo-glycemic episodes) throughout the day (Figure 3). A couple of glucose

measurements prior to exercise, spaced 15-45 min apart, are recommended to identify patterns and trends. Ideally, blood glucose checks should be made every 30 min during physical activity so that strategies can be operated at the need. Even in the late recovery, glucose readings are important because of the increased insulin sensitivity occurring 7-11 hours post-exercise [46].

Continuous glucose monitoring (CGM) systems use a small sensor, inserted under the skin, that provides interstitial glucose readings as often as once per minute over a 24 h period. The sensor stays in place for several days up to a week, then it must be replaced. The measurements are transmitted to a wireless monitor, which allows gathering trends, particularly useful to reconstruct patterns modulated by exercise. However, real-time CGM tends to overestimate blood glucose levels in the low range, due to the 10-20 min lag time between interstitial fluid and capillary glucose. This is notably alarming if hypoglycemia is developing, although short-term use of CGM with alarms has been shown to reduce the incidence and duration of hypoglycemia to a certain extent [72]. In another study [73], CGM revealed to be accurate despite markedly different metabolic and exercise conditions (high-intensity intermittent exercise versus continuous moderate). The coupling of CGM with insulin pump (continuous subcutaneous insulin infusion, CSII) has been proved to be efficient in gaining the beneficial effects of exercise in the management of T1D [6]. The CSII is a (relatively recent) technological breakthrough in the T1D therapy, as it allows to simulate the physiologic pancreatic secretion of insulin by delivering rapid-acting insulin analogs throughout the day. With respect to multiple daily insulin injections (MDII), CSII offers a larger flexibility and a more accurate insulin administration so much as for tiny doses: both bolus insulin and the basal infusion rates can be adjusted by the users before, during, and after exercise. CSII is

definitively advantageous as the basal insulin reduction following exercise can occur automatically during sleep, so to help prevent nocturnal hypoglycemia [48]. Furthermore, the introduction of new ultra-long acting basal insulins (insulin degludec, insulin glargine U-300) may substantially reduce dosing frequency because of their ultralong action profile (lasting >24 h and possibly up to 40 h), resulting in improved mental well-being scores [74] and, ultimately, in a drecreased incidence of hypoglycemia compared to their rival basal insulin analogs [75]. However, whether these new insulins may be efficacious, in relation to the exercise timing, remains to be elucidated.

Although the risks of hypoglycemic events cannot be totally excluded even under the strict control operated by CSII plus CGM, this latter combination represents one of the most promising automated model toward the pathway to the artificial pancreas.

Apart from closed-loop control systems or artificial pancreas, islet transplantation (IT) has become a desirable scenario, whenever possible, on numerous scientific and clinical fronts in the therapy and management of T1D [76]. IT restores glycemic control awareness and offers protection against severe hypoglycemia, at least in the mid-term after trasplant [77]. As to the exercise benefits, β-cells transplanted recipients have tremendously improved their medical outcome and lifestyle factors (i.e. insulin-independence, above all) even under conditions of ultra-endurance training [8, 78].

With all these technological advances, at the other end of the spectrum, there is actually a quite bit of evidence that adequate lifestyle education and training to all people with T1D are still poor. Few parallel studies have investigated the rates of diabetes education in exercise, and T1D patients have harsh access to certified

programs on diabetes self-management training, especially outside of major urban areas. Optimal diabetes control will certainly be achieved thanks to breakthrough technologies; however, at the simpler level, much more can yet be done on dissemination of adequate lifestyle education and adherence to treatment recommendations. This is also true when it comes to to exercise benefits in T1D.

5. Aerobic exercise in T1D

When glycemic control is not deteriorated in individuals with T1D, endurance training will likely induce the same adaptions to which healthy subjects normally respond to. Therefore aerobic training improves insulin sensitivity, blood lipid profile, physical fitness; increases energy expenditure; decreases blood pressure, risk of CVD; enhances psychological well-being. These adaptations are still appreciable even though glycemic control is not improved. Ultimately, long-term health and life expectancy will be favorably impacted by regular aerobic exercise even under conditions of impaired glycemic control. For these reasons, in the management of T1D, the goal of optimal blood glucose control is of paramount relevance. However, a decent glycemic control permits to achieve an elite level of sport performance. In a long-distance runner, β-cells transplanted, a high volume of aerobic training not only was compatible with the treatment of T1D, but also it counteracted diabetic symptoms and mitigated the side effects of immunosuppressive drugs and graft dysfunction over a 10-year observation [8, 78]. In a study on 10 triathletes with T1D, endurance performance was unaffected over 3 years, despite typical glycemic dysregulation through the race [79]. A normal cardiopulmonary peak was reported in adults with long-standing T1D, in a good glycemic control.

T1D adolescents have shown to have an aerobic capacity 20% lower than peer-matched healthy controls [80]. A reduced maximal aerobic capacity has been reported in young patients with T1D with respect to their non-diabetic peers. Physical work capacity seems to be related to the level of glycemic control, which in turn explains, to some extent, athletic and sport skill performance. It is still uncertain whether reduced work capacity in young subjects with T1D results from poor oxygenation [81], low muscular capillarization [82], or if poor metabolic control depends on low regular physical activity [83].

According to the "American Diabetes Association" position statement [84, 85], children and adults should perform at least 60 min or more of moderate-to-vigorous intensity, daily. Adults should be recommended to exercise at least 150 min/week for 3-7 days per week (with no more than 2 consecutive days of rest) at moderate-to-vigorous intensity (50-70% of maximum heart rate; 50-85% of VO_2max). Adults able to run at about 10 km/h may diminish the aforementioned duration, by running 75 min/week (subjectively "vigorously") on at least 25-min block.

6. Resistance exercise in T1D

Resistance exercises are based on the use of muscular strength to move a weight or work against a resistant load to a maximal extent (strength, force) or repeatedly (muscle endurance). Such training not only improves musculoskeletal health but it helps to maintain independence in carrying out daily activities, with reduced risk of injuries.

Muscular mass and strength can be positively enhanced by resistance training in individuals with T1D. The effects of resistance exercise on glycemic control in T1D are still controversial, not univocally ascertained, but promising. For

instance, resistance training has been shown to be effective in minimizing risk of hypoglycemia post-exercise in T1D [86]. Prior to neuropathic complications, skeletal muscle abnormalities have been observed in T1D patients, suggesting the existence of a typical diabetic myopathy in humans [83]. Decrements in musculo-skeletal strength, loss in muscle fiber size, and increase in glycolytic enzymes and fast-twitch fibers have been reported in individuals with T1D. Others have shown slower conduction velocity and motor unit discharge frequency during muscular isometric contractions in T1D [87]. These factors, along with higher glycolytic flux (e.g. muscle glycogen as preferred energy source), early dehydration and acidosis [88], might promote early fatigue in these T1D populations (both pediatric- and adult-).

Hence, appropriately orchestrated resistance training programs may counteract this mass remodeling detrimental for the metabolism of T1D subjects. Types of resistance training may include weight lifting (free weights), specific isotonic machines, bands, isometric exercises and calisthenics.

"American Diabetes Association" recommends adults to perform moderate (15 repetitions at maximum effort) to vigorous (repetitions at maximum effort) resistance activities, 2-3 days/week on non-consecutive days. At least 8-10 exercises with completion of 1-3 sets of 10-15 repetitions near to fatigue per set [85]. Conditioning of the body core and balance training (time standing on a definite position) are as well envisaged. Children and youth should incorporate such muscle-conditioning activities as part of their daily play, games, recreation, physical education, family context. Importantly, these activities should exceed the sedentary time, by accumulating planned and structured physical effort in the course of daily living.

Whatever the primary goal of the training will be, either improvements in functional capacity or increased ability to care for oneself, the resistance program should anyway consider the possible presence of chronic comorbidities typical of the disease (neuropathy, vascular damage, CVD). Such health concerns ought to be medically addressed before engaging in resistance training.

7. Exercise defense against syndromic inflammation in diabetes

Several studies documented elevated circulating inflammatory and oxidative stress markers in patients with T1D. On a side, oxidative stress may be seen as a characteristic trait of T1D, on the other one, hyperglycemia can exacerbate this scenario of systemic inflammation. T1D patients exhibit numerous features of atherogenesis, including activation of transcription factors stimulating expression of proinflammatory cytokines. In reality, a vast array of conditions threatens the functionality of the β-pancreatic mass, promoting islet inflammation and metabolic stress/imbalance. It is possible that increased stimulation of the β-cells due to overfeeding, obesity, insulin resistance, psychological stress, infections, and low physical activity, stimulate or sometimes even initiate the autoimmune attack leading the insulin-producing islet-cells to the their failure. Exercise triggers a cytokine response that may be anti-inflammatory and offers protection to β-cell against all these insults.

Depending on intensity, type and duration, physical exercise is a potent modulator of physiological changes at different levels, pertaining stress hormones, energy crisis and oxidative stress. Regularly exercising at moderate intensity has been shown to enhance the antioxidant defense system, thus reducing the oxidative stress. To a variable degree, as already observed in other chronic

inflammatory conditions, these exercise-related adaptations may express a favorable cytokine pattern and may preserve the β-cell redox homeostasis – and thus its insulin secreting capacity – against the multiple-origin attacks directed towards β-cells. However, inconclusive data have been reported on exercise-induced cytokine response (TNF-α, IL6) with a putative beneficial health effect. According to our observations, physical exercise may be helping in two way by both enhancing insulin sensitivity (increasing insulin action) and β-cell function through the reduction of the deleterious effects of autoimmunity. These two effects are likely to combine together and produce a substantial gain in glucose tolerance [4].

8. Integrative view

Multiple improvements in health indicators firmly remark that regular exercise is essential in the management and lifestyle of people with T1D (Table 2). Nevertheless, given the endocrine responses to exercise in T1D are blunted and inadequate, clinicians and exercise professionals must allow discretion when prescribing physical activity. Exercise programs should be meticulously based on close monitoring of physical activity and the body's response in terms of glycemic fluctuations and inflammatory or oxidative parameters.

Statement of Human and Animal Rights

This article does not contain any studies involving human or animal subjctes performed by any of the authors.

Conflict of Interest

The authors declare that they have no conflict of interest.

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Figure Captions

Figure 1.

Graphical Abstract. The pillars to maximize exercise-benefits in the lifestyle of people with type 1 diabetes: properly modulating carbohydrates ingestion before-during-after exercise, strict monitoring of glucose and insulin, adequacy of healthcare professionals, and a comprehensive educational approach.

Figure 2.

Synoptic picture summarizing the metabolic and endocrine responses to moderate, constant-load exercise in healthy- and T1D-subjects.

Figure 3.

Scheme of the indications (nutritional and insulin adjustments) for maintaining glucose homeostasis during constant-load, moderate exercise in T1D-subjects according to the most reported guidelines [85, 89, 90].

Table 1.

Studies examining the effects of exercise interventions on T1D.

Authors	Subjects	Type of exercise	Main outcomes
Andersen et al.[91]	Adults with T1D	Isokinetic peak torque of dorsal/plantar flexion of ankle	Torque loss at ankle and knee neg. correlates with neuropathy
Andreassen et al.[92]	Adults with T1D	Peak torque	Torque correlates with muscle volume
Campbell et al.[93]	Male adults on MDI, with CGM	45' treadmill running	Preventing post-exercise hypoglycemia with ↓basal insulin and ↓prandial bolus insulin
McAuley et al.[94]	Adults with T1D on CSII	30' moderate-intensity stationary bicycle, 60' after ↓ post-basal	Exercise-induced hypoglycemia was prevented only with↑insulin basal rate supplemental CHO
Luzi et al.[3]	Adults with T1D	Regression analysis on between autoimmunity markers (GAD, IA) and weekly energy expenditure (EE) derived from physical exercise	↓autoimmunity and longer honeymoon in ↑physycally active subjects
Sherr et al.[95]	Adolescents and young subjects with T1D	60 min treadmill walking @ 65-70% HRmax	↓nocturnal hypoglycemia w/ closed-loop insulin delivery, regardless of activity level in the mid-afternoon
Martinez-Ramonde et al.[96]	Diabetic adults from onet to 2-yr period	Retrospective diary on PA programmes adherence	↑PA allows better glycemic control, residual pancreatic mass and insulin requirements
Adamo et al.[6]	Adults with T1D on CSII + CGM	3 mo observational study on PA levels	↑PA allows better metabolic control and body composition, ↓hypoglycemic events
Davey et al.[97]	Adolescents with T1D	Hyperinsulinemic euglycemic clamps during either resting or 45 min cycling on an ergometer @ ~ 65% VO_2max	No evidence of biphasic pattern of post-exercise risk of hypoglycemia
Tunar et al.[98]	Adolescents with	12-wk of Pilates session	↔ HbA1c, ↑peak power,

	T1D		↑mean power, ↑vertical jump and ↑flexibility
Yardley et al.[99]	Adolescents and adults with T1D	RE on aerobically active subjects. 3 times/wk; 8RM x 7 exercise on weight machines	PA recommendations for subjects with T1D. READI study has not been completed yet.
Bally et al.[71]	Young male adults with T1D	High-intensity intermittent training versus continuos moderate-intensity exercise	↓Glucose disposal and ↑flexibilityin high-intensity intermittent training
Shetty et al.[100]	Young adults with T1D	Euglycemic clamps during and for 2-hr after different intensity exercise (35-80% O_2 peak)	Inverted U relationship between exercise intensity and glucose requirement
Davey et al.[101]	Young adults with T1D	Hyperinsulinemic-euglycemic clamp during and for 8-hr after 30 min of moderate-intensity exercise on two separate occasions followed by either a 10-s maximal sprint effort or no sprint	↔ CHO after 10-s sprint to maintain euglycemia
Yardley et al.[68]	Young adults with T1D	AE (45 min running @ 60% VO_2 peak) before RE (3 sets x 8-7 different exercises) or vice versa	RE before AE improves glucose stability dufing exercise and ↓ hypoglycemia post-exercise
Guelfi et al.[69]	Young adults with T1D	Euglycemic clamps during Moderate-intensity exercise (30 min cycling @ 40% VO_2peak) versus intermittent high-intensity exercise (30 min continuous exercise @ 40% VO_2peak interspersed with additional 4-s maximal sprint efforts performed every 2 min)	Decline in blood glucose in the early recovery is less with high-intensity intermittent exercise vs moderate one
Iscoe et al.[70]	Trained athletes with T1D	Interstitial glucose levels measured during two sedentary days and during 2 days in which 45 min of afternoon continuous moderate-intensity exercise occurred either with or without intermittent high-intensity exercise	↓Nocturnal hypoglycemia with intermittent high-intensity exercise + moderate one
Harmer et al.[64]	Young adults with T1D	Sprint training (cycling @ 130% VO_2 peak) for 7-wk.	↓metabolic destabilization (of lactate, H^+, glycogenolysis/glycolysis, and ATP) during intense exercise, ↑ Muscle

			oxidative metabolism
Komatsu et al.[80, 102]	Children, adolescents, and young adults with T1D	incremental aerobic exercising test on a motorized treadmill	Aerobic capacity 20% ↓ in T1D vs peer controls
Veves et al.[103]	Young adults with T1D	Observational study between physically active and sedentary subjects	Aerobic capacity ↔ in physically active people with T1D
Gusso et al.[104]	Adolescents with T1D, T2D and obese	Evaluation of maximal aerobic capacity on acycle ergometer during submaximal exercise	↓Exercise stroke volume response and ↓aerobic capacity in diabetic adolescents
Salem et al.[105]	Adolescents with T1D	Mixed exercise programs (AE+RE) 3 times/wk for 6 mo	↓HbA1c, ↔hypoglycemic episodes, BMI improved, ↓insulin requirements, dyslipidemia improved
Codella et al.[8]	An islet-transplanted ultra endurance runner	Monitoring of glucose, insulin, autoimmunity and inflammatory markers before, during and after marathon periods	Marathons were accompanied by marathon'' period was accompanied by ↓HbA1c, ↓exogenous insulin requirement, ↔autoimmune profile, with systemic inflammation
Herbst et al.[106]	Children and adolescents with T1D	Self-reported regular physical activity	↓total cholesterol, ↓low-density lipoprotein cholesterol, ↓triglyceride levels
Huber et al.[107]	Children and adolescents with T1D	Two training sessions (lasting 90-120 min) per d (soccer, biking, hiking, swimming, ball games)	↓in mean insulin dosage, ↓mean HbA1c, ↓total ghrelin levels
Laaksonen et al.[108]	Adults with T1D	30-60 min moderate-intensity running 3-5 times/wk for 12-16 wk.	Better body composition, ↔HbA1c, better lipid profile

Abbreviations: ↑ = significant increase; ↓ = significant decrease; ↔ = no changes; AE = aerobic exercise; CHO = carbohydrates; d = day; HR = heart rate; min = minutes; mo = month; PA = physical activity; RE = resistance exercise; 1RM = repetition maximum; s = second; T1D = type 1 diabetes; VO_2 = oxygen uptake; yr = year; wk = week.

Table 2.

Differences between sedentary and active subjects with type 1 diabetes

	sedentary	active
body composition [6, 109]	–	+
blood glucose control [6, 8, 110, 111, 96, 112]	=/–	=/+
hypoglycemic episodes [6, 8, 48, 97, 93]	=/–	–
hyperglycemic episodes [55, 56, 113]	=/–	+
insulin doses [6, 8, 93]	–	+
insulin sensitivity [7, 31, 46, 84]	–	+
blood lipid profile [111, 112]	=/–	=/+
autoimmunity [3, 114, 115]	–	=/+
inflammation [96, 115–118]	–	=/+
psychological well-being [112, 119]	=/–	+
cardiorespiratory fitness [80, 102, 104]	–	+

= stable

+ improvement

– deterioration

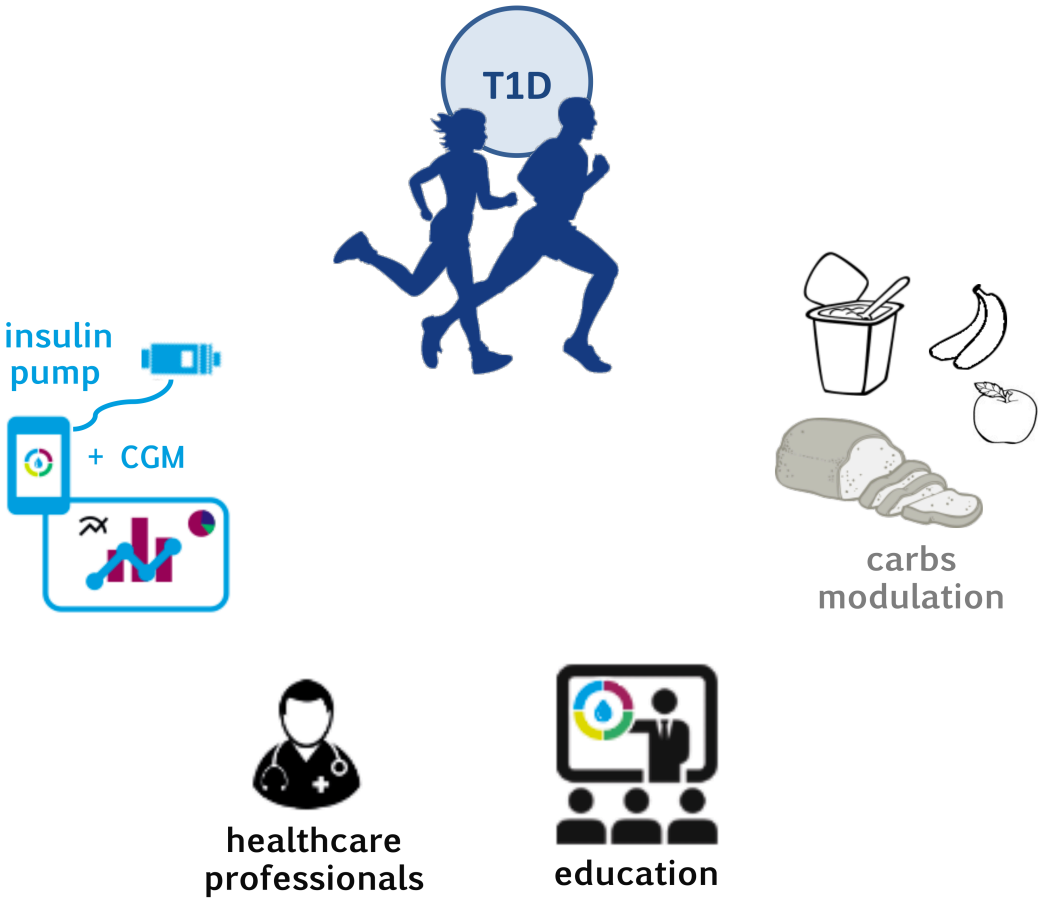


Figure 1.

Graphical Abstract. The pillars to maximize exercise-benefits in the lifestyle of people with type 1 diabetes: properly modulating carbohydrates ingestion before-during-after exercise, strict monitoring of glucose and insulin, adequacy of healthcare professionals, and a comprehensive educational approach.

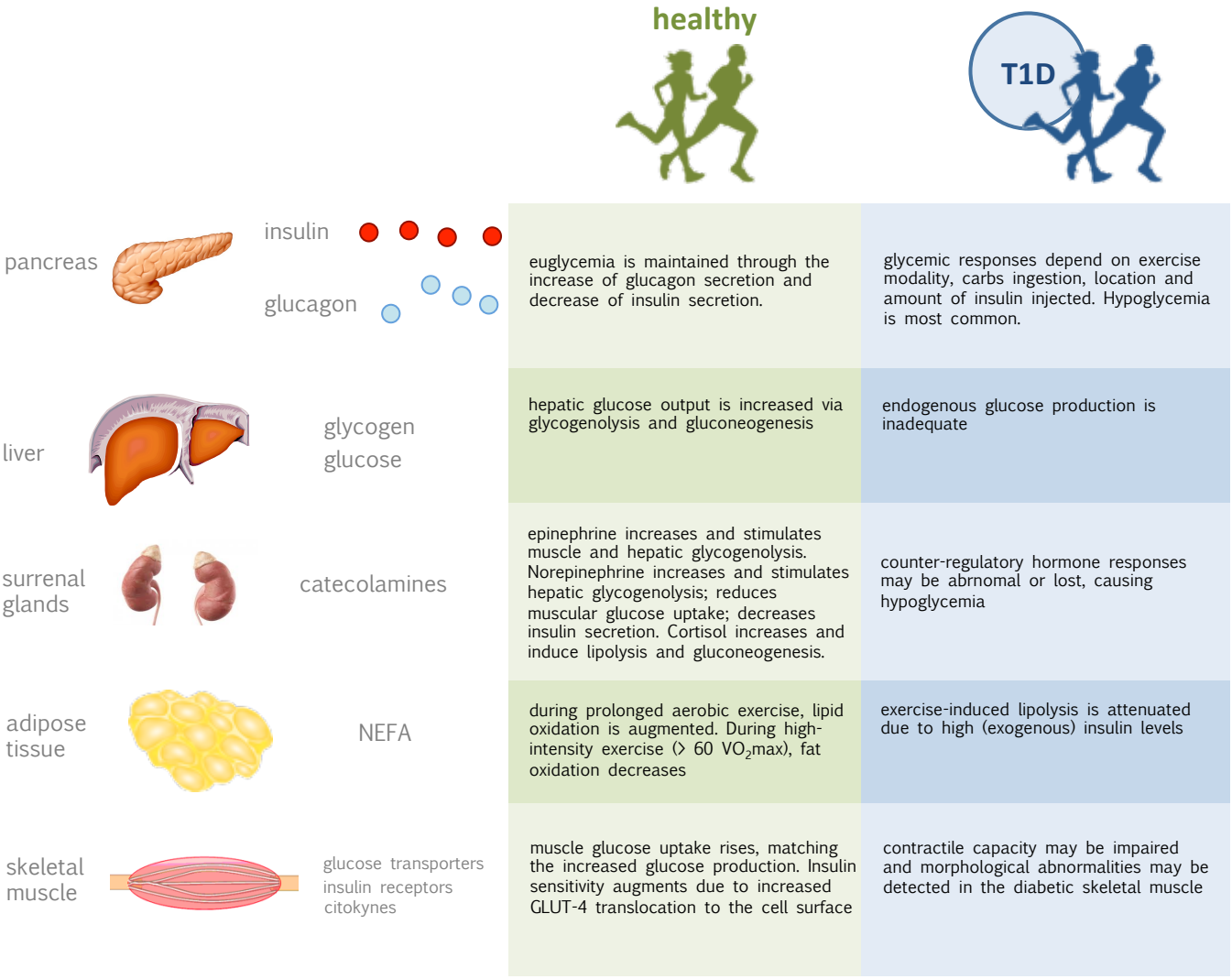
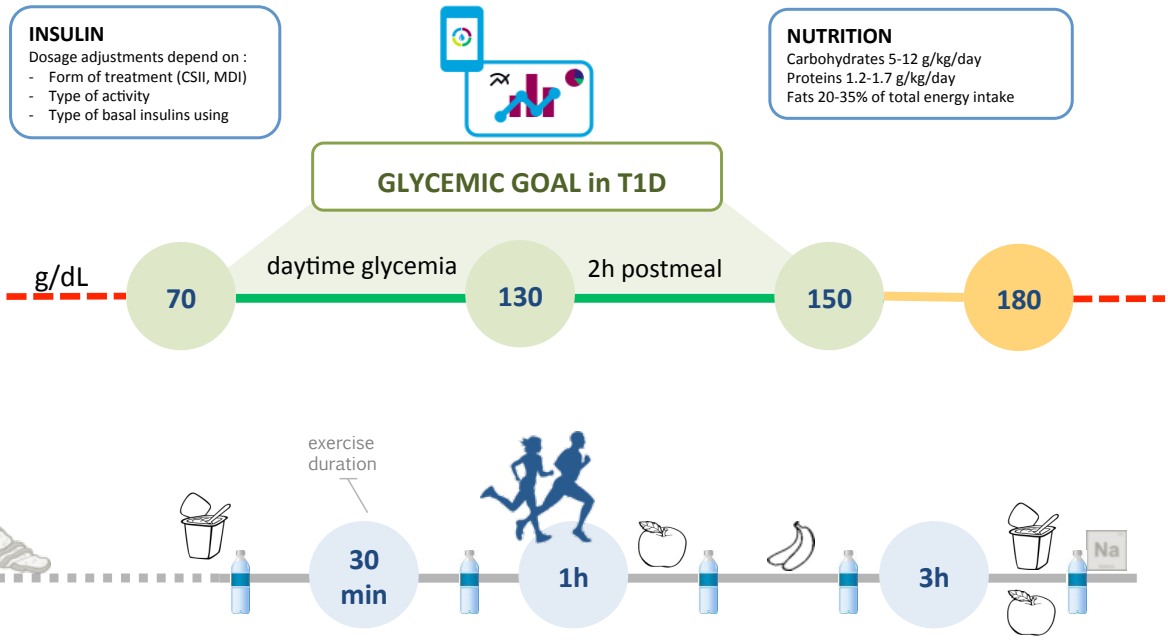


Figure 2.

Synoptic picture summarizing the metabolic and endocrine responses to moderate, constant-load exercise in healthy- and T1D-subjects.



ADJUSTMENTS	Before exercise	During exercise	Prevent post-exercise hypoglycemia (after moderate to high intensity exercise of >2hours)
NUTRITION	BG<126 mg/dL → 15-30 g CHO BG≥180 mg/dL → delay CHO intake exercise duration <45' → ~15g CHO, 15-30' before prolonged exercise → 1g CHO/kg, 1h before	hydratation 30-60g CHO/exercise-hour if >70g CHO/exercise-hour needed glucose:fructose ratio should be 2:1	within 30 min → 1.5 g CHO/kg at 2h intervals up to 6h after exercise → 1.5 g CHO/kg
INSULIN	reducing bolus (especially if exercise is within 90-120' of a bolus) adjusting basal insulin rate (on CSII, set boluses every hour – 50% of the usual hourly basal rate)	adjusting basal insulin rate (CSII)	reducing basal insulin rate (CSII and MDI therapy) lesser insulin reduction if exercise duration > 3h from last injection of rapid insulin decreasing boluses administered within 1h after exercise

Figure 3.

Scheme of the indications (nutritional and insulin adjustments) for maintaining glucose homeostasis during constant-load, moderate exercise in T1D-subjects according to the most reported guidelines [85, 89, 90].