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Exercise and Type 1 Diabetes Mellitus

Bewegung und Diabetes mellitus Typ 1

Summary

- ▶ **Regular physical activity** optimizes cardiometabolic as well as musculoskeletal health and improves cognitive and psychosocial functioning in people with type 1 diabetes mellitus (T1DM). Physical activity and exercise should therefore be promoted for all people with T1DM. Unfortunately, people with T1DM often avoid engaging in sports activities because of concerns of hypoglycemia and metabolic fluctuations. They must consider a variety of factors when planning to exercise (insulin therapy, food intake, stress, time of day, etc.).
- ▶ **Pharmacological and technological innovations** in recent years have made exercise easier for people with T1DM. For example, continuous glucose monitoring allows for better treatment decisions, taking current sensor glucose levels and trend arrows into account. Support from qualified and motivated diabetes teams and sports therapists/ trainers is needed to ensure that as many people with T1DM as possible benefit from the positive effects of sport and exercise.

KEY WORDS:

Sports, Physical Activity, Glucose Management, Insulin, Hypoglycemia, Metabolic Fluctuation

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Introduction

Type 1 diabetes mellitus (T1DM) is an autoimmune disease characterized by progressive destruction of the insulin-producing beta cells of the pancreatic islets. The resulting insulin deficiency necessitates lifelong insulin substitution.

The incidence of T1DM has increased rapidly in recent decades and is currently estimated to be 15 per 100,000 people per year (13).

Physical activity and exercise are an important component in the lives of many people with T1DM. Young children follow their natural urge to exercise. Children, adolescents, and adults often continue to pursue their favorite activities despite diabetes, to discover new sports, compete in sports with like-minded people, and most importantly, to have fun. As people age, the preventive or rehabilitative health aspects of physical activity gain importance. Finally, sport serves as an important social factor of integration in nearly all phases of life (3, 11).

Pathophysiology

Glucose regulation in metabolically healthy individuals is mediated by the peptide hormone insulin and its counterpart glucagon. Insulin causes activation and translocation of glucose transporters (GLUT-4) to the muscle membrane via the insulin signaling cascade, enabling the uptake of glucose into the muscle cells. Glucagon causes a release of glucose from the liver (gluconeogenesis). The contra-insulin hormones epinephrine, norepinephrine, and cortisol also drive gluconeogenesis. Furthermore,

muscle contractions cause glucose to be taken up into muscle cells via an insulin-independent signaling pathway (as in insulin-dependent glucose uptake via GLUT-4) (11).

People with T1DM lack endogenous insulin secretion. Counterregulatory glucagon secretion is usually impaired as well. Excessive administration of insulin in the absence of sufficient dietary glucose intake thus increases the risk of exercise-induced hypoglycemia in patients with T1DM. Post-exercise insulin sensitivity is increased and glucose uptake enhanced when the muscle begins to replenish glucogen reserves. This effect can last up to 48 hours (11).

Without appropriate adjustment of insulin administration or external glucose supply, dangerous hypoglycemic situations may occur in individuals with T1DM, even during the recovery phase. On the other hand, in the presence of insulin deficiency, e.g. by skipping insulin injections, the risk of developing a life-threatening ketoacidosis might increase, which can be further intensified by physical activity with the release of insulin's counterregulatory hormones (11).

Appropriate adjustment of insulin administration and food intake therefore represents a great challenge for athletes with T1DM in light of the complex pathophysiological mechanisms.

Benefits and Risks

Physical activity in people with T1DM has been shown to have beneficial metabolic, cardiovascular, musculoskeletal, cognitive as well as psychosocial



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effects. In addition, physical activity has been shown to reduce all-cause mortality and disease-related mortality (12, 21).

By contrast, there are potential risks of acute hypo- or hyperglycemic activity-associated metabolic disturbances, musculoskeletal injuries, and risks of exercise-induced cardiovascular events or of deteriorating microvascular diabetes-associated organ complications (e.g. diabetic retinopathy) (21).

However, the health benefits indisputably outweigh the risks. People with T1DM should be regularly encouraged to be physically active and to exercise, as this has substantial health benefits (19, 29).

General Physical Activity Recommendations

In line with the practice guidelines of the German Diabetes Association (11), children and adolescents with T1DM should be active for at least 60 minutes/ day at moderate to vigorous intensity, while strength training is also recommended at least 3 days/ week. It is recommended that adults with T1DM generally exercise at least 150 minutes/ week at moderate to vigorous intensity. Alternatively, for younger and fitter individuals, high-intensity interval training (at least 75 minutes/ week) may be sufficient. In addition, 2-3 sessions of strength training/ week on non-consecutive days are recommended. Aside from reducing sitting time, older individuals with T1DM, in particular, should engage in flexibility and balance training 2-3 times per week. Yoga and Tai Chi can improve flexibility, muscle strength, and balance (9, 11). The recommendations for physical activity do not fundamentally differ from those for people without diabetes.

Barriers

Most T1DM patients, however, fail to implement the above recommendations (19). A recently published meta-analysis concludes that children and adolescents with T1DM are less active, have longer sitting times, and lower levels of cardiovascular fitness compared with their healthy peers (15).

The primary reasons for this are concerns about acute metabolic disturbances, diabetes-associated organ complications, and chronic illness behaviors such as overprotection and a loss of confidence in their own body's capacity. In general, the barriers to physical activity are similar to those among non-diabetic people (lack of time, inadequate physical activity environments, psychosocial and physical barriers) (3, 16, 19).

Current data suggest that the use of new technologies, such as continuous glucose monitoring (CGM), is reducing concerns of hypoglycemia as a reason by people with T1DM to avoid exercising (14). It is also the physician's duty to encourage the patient and break down such barriers by giving advice and clarifying certain aspects.

Medical Examinations Before Participation in Sports Activities

Adults with T1DM are at higher risk of developing (subclinical) coronary artery disease (18). Screening of cardiopulmonary asymptomatic individuals who exercise at low to moderate intensity has not been shown to reduce the risk of cardiac events (28). The recommendations of various scientific societies differ primarily on the question whether cardiac diagnostics should even be performed in asymptomatic patients before planned low- or moderate-intensity activities (7, 18, 23, 28). The consensus is that cardiovascular risk factors and atypical symp-

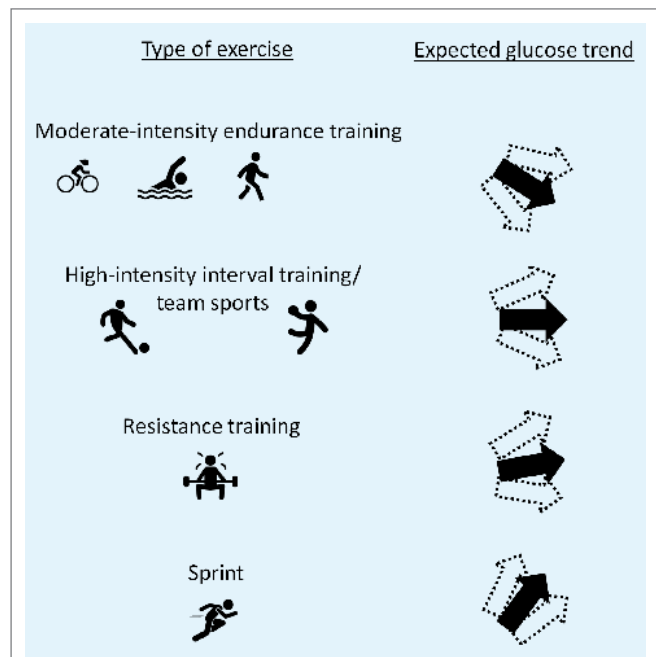


Figure 1

Glucose trends in response to different types of exercise (modified figure based on (21)). Graphics: freepik.com.

toms of coronary artery disease should be carefully recorded in the patient's medical history to assess their individual risk profile. Furthermore, other relevant diabetes-associated organ complications (peripheral arterial disease, retino-, neuro- and nephropathy, diabetic foot syndrome, Charcot arthropathy) must be considered in the planning of physical activities (7,9). In addition, cardiovascular diagnostics should, in any case, be carried out prior to starting a high-intensity exercise program. This usually includes an electrocardiogram, echocardiography and ergometry at the discretion of the clinician (28). An exercise electrocardiogram (during the mentioned ergometry) and blood pressure measurements at rest and during the ergometry could be added as important diagnostic tools.

Factors Affecting the Metabolic State

Blood glucose responses show a very high inter-individual and sometimes also an intra-individual variability, especially in the context of physical activity (19). In addition to physical activity type (figure 1), a variety of factors affect individuals' metabolic situation (table 1) (1, 6, 11, 19, 21).

In addition to a good understanding of essential treatment principles, one prerequisite for safely engaging in sports activities is good metabolic control under everyday conditions. Non-physiological therapy algorithms or an incorrectly programmed basal rate make optimal metabolic control in exercise impossible. It is therefore recommended that athletes with T1DM, in particular, participate in appropriate seminars (dealing with multiple dose injection (MDI)- and/or continuous subcutaneous insulin infusion (CSII) therapy, and/or CGM training, and/ or sports seminars for people with T1DM) (3). Keeping a sports diary also represents a viable option for analyzing individual metabolic dynamics (11).

Glucose and Ketone Measurements

Closely meshed glucose monitoring before, during and after sports activities is essential for safe and optimal metabo- ➤

Table 1

Examples of factors that influence glucose metabolism during exercise (1, 6, 11, 19, 21).

FACTORS
Type of exercise, duration and intensity
Time of season
Training status
Competition stress
Baseline glucose level, glucose trend, ketonemia
Diabetes duration, C-peptide status
Previous hypoglycemic episode(s)
Insulin resistance
Active insulin (IOB)/ last insulin administration
Diabetes therapy (types of insulin, ICT, MDI, CSII)
Last food intake (timing, macronutrients)
Previous sports activities
Cardiorespiratory fitness
Body status (body weight, lean mass, hydration)
Sex
Menstrual cycle (women)
Time of day
Environmental conditions (heat, cold, humidity)
Emotional status
Sleep duration, sleep quality

Table 2

Elevated blood ketone levels and exercise recommendations (19).

BLOOD KETONE LEVEL	EXERCISE RECOMMENDATION
0.6-1.4 mmol/l	At most, light-intensity physical activity (<30 minutes), corrective insulin dose if appropriate
≥ 1.5 mmol/l	Contraindicated, metabolic recompensating measures should be initiated

lic control.

While capillary blood glucose measurements only indicate the current glucose status, rtCGM (real-time continuous glucose monitoring) systems also display the current glucose trend (i.e. whether glucose is stable, rising or falling) (24).

However, rtCGM systems record the glucose concentration in the individual's interstitial fluid and not directly in the blood. If rapid changes in glucose occur during physical activity, blood and tissue glucose values can (which is physiologically explainable) deviate considerably from one another ("time lag") (1).

Previous therapy recommendations for exercise in T1DM are based on capillary blood glucose measurements. A joint position paper of the European Association for the Study of Diabetes (EASD) and the International Society for Pediatric and Adolescent Diabetes (ISPAD) presents detailed recommendations on therapy adjustments in sports activities, taking different variables of continuous glucose monitoring into account. The inclusion of glucose trends (trend arrows) is crucial in therapy management when engaging in sports activities (17).

Tests for ketone bodies should ideally be performed as blood ketone determinations (1).

Therapy Adjustments

Depending on the type of exercise and influencing factors mentioned above, glucose levels of between 126 and 180 mg/dl (7 and 10mmol/l) are usually targeted before and during exercise (17, 19).

Anaerobic and high-intensity exercise sessions can start at a lower glucose level (90-124mg/dl [5-6.9 mmol/l]) when appropriate, if a drop in glucose concentration is not expected.

If glucose levels above 270mg/dl (15.0 mmol/l) cannot be properly explained, a ketone analysis should be performed: if the T1DM individual's blood ketone levels are low (<0.6 mmol/l), they can engage in light to moderately intense aerobic exercise. If the person's blood ketone levels are slightly elevated (up to 1.4 mmol/l), they should at the very most engage in brief exercise (<30 minutes) of mild intensity. A small corrective insulin dose may be required before starting to exercise. Any exercise activity is contraindicated at blood ketone levels of ≥1.5 mmol/l. In that case, metabolic recompensating measures should be initiated (19, 21) (table 2).

Because of the muscle filling effect, a reduction of the insulin dose (bolus and basal insulin) may be necessary, depending on the previous activity up to 14 hours after the end of the activity (11).

In principle, there are two adjusting mechanisms for metabolic control before, during and after physical activity: (i) the intake of additional carbohydrates, (ii) and/ or a reduction in insulin administration (figure 2).

There are various options for insulin dose adjustment depending on the type of therapy (MDI, CSII or automated insulin delivery (AID)) and the expected glucose trend. As a rule, active insulin (insulin on board – IOB) should be kept as low as possible in all types of therapy (table 3) (19, 21).

When using an AID system, an algorithm continuously adjusts the insulin pump's insulin delivery based on CGM data. Preliminary results on physical activity and the use of an AID system suggest a modest improvement in time-in-range (TIR) glucose values compared with standard care (8). Current real-world data on adults with T1DM (also for those using an AID system) show an improvement in glucose values in the target range (TIR) on exercise days (endurance as well as interval and strength training) compared to inactive days in adults with T1DM, but an increase at the same time in glucose values below the target range (time below range - TBR) (20). The safe and profitable use of an AID system requires basic as well as product- and system-specific knowledge (1, 11). Timely information on physical activity 90-120 minutes prior to the start of an exercise session is crucial. There should be no carbohydrate intake immediately before exercising, because if the (predicted) glucose value exceeds the target value set by the system, the algorithm will undesirably increase the insulin pump's insulin delivery. Consequently, only small amounts of carbohydrates should be consumed (continuously) during exercise. The AID systems incorporate different sports modes. Furthermore, they include a system-specific option to adapt insulin sensitivity and the insulin-carbohydrate ratio to the type of exercise activity being performed (1, 11, 26).

Exercise and Diabetes-Associated Organ Complications

In addition to common sports injuries such as ruptured ligaments and stress fractures that many athletes experience, athletes with diabetes have an increased incidence of tendinopathies, joint capsulitis (especially adhesive capsulitis of the

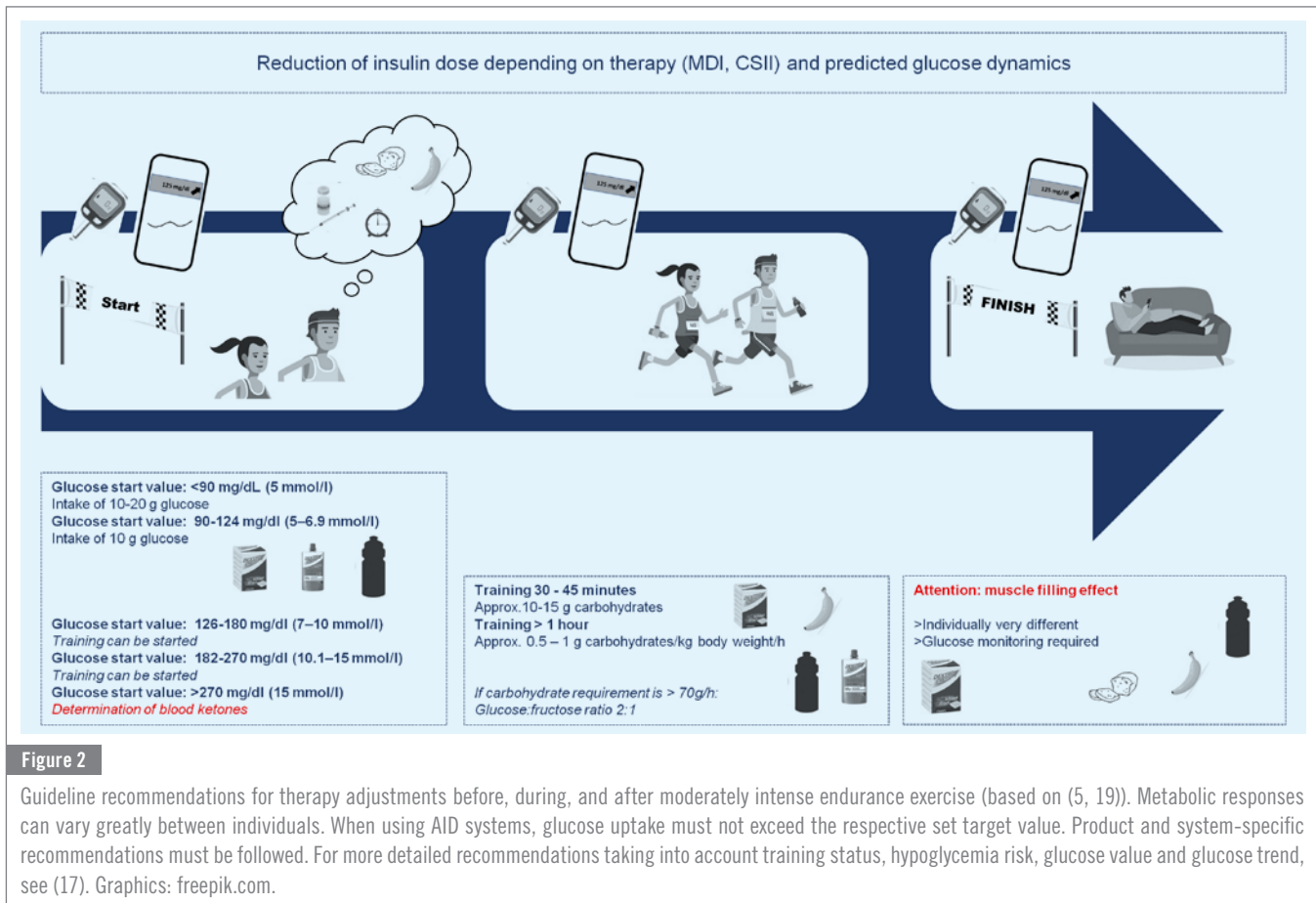


Figure 2

Guideline recommendations for therapy adjustments before, during, and after moderately intense endurance exercise (based on (5, 19)). Metabolic responses can vary greatly between individuals. When using AID systems, glucose uptake must not exceed the respective set target value. Product and system-specific recommendations must be followed. For more detailed recommendations taking into account training status, hypoglycemia risk, glucose value and glucose trend, see (17). Graphics: freepik.com.

shoulder), and articular cartilage disease. In addition to the accumulation of advanced glycation end products (AGEs), reduced tissue perfusion and nerve damage explain the particular risk of injuries and diseases of the musculoskeletal system (28).

To be able to make risk-adapted exercise recommendations, potential micro- and macrovascular diabetes-associated complications must be considered. Examples include (7, 11, 27): the presence of cardiovascular complications such as coronary artery disease, heart failure, and/ or peripheral arterial disease, which require concomitant cardiology care. In the presence of sensorimotor neuropathy and/ or diabetic foot syndrome, attention should focus on wearing diabetes-appropriate sports shoes; activities that have a high impact on feet are only possible under close monitoring. Such activities are contraindicated if a diabetic foot lesion (Wagner stage ≥ 1) or an active diabetic osteoarthropathy is present. In case of autonomic neuropathy, disruption of physiological blood pressure and heart rate regulation must be considered. A cardiological screening prior to starting physical activity is required. Patients with T1DM and chronic kidney disease benefit from physical activity. Blood pressure increases above 180-200/100mmHg should be avoided in patients with proliferative retinopathy. High-intensity strength or endurance training as well as combat sports are unsuitable and potentially harmful for patients with retinopathy. More detailed as well as further recommendations and precautionary measures can be found in (7, 11).

The presence of a hypoglycemia perception disorder requires maximum attention, and even more so during exercise.

In addition to inadequately high insulin levels or insufficiently filled glycogen stores, impaired neuroendocrine and metabolic glucose counterregulatory mechanisms increase

the risk of exercise-induced hypoglycemia in people with T1DM, especially in people who have had diabetes for a long time.

Episodes of previous hypoglycemia exacerbate the counterregulatory dysfunction, which may develop into a dangerous vicious cycle for athletes with T1DM (10).

Competitive and Extreme Sports

People with T1DM can, in principle, participate in any sports, including competitive sports. However, sports that entail an increased risk due to impaired consciousness or judgment as a result of hypoglycemia, such as diving, skydiving or extreme climbing, are less suitable for T1DM patients. For this case, people with T1DM must have many years of personal experience, be very cautious, and prioritize individual planning (11).

Device-specific (rtCGM, CSII, and AID systems) requirements for special altitude, climate, and water pressure conditions must be considered as well.

The list of successful competitive athletes including Olympic champions with T1DM is long. To achieve maximum mental and physical performance, glucose levels must be close to normal during training and competition (22).

Activities of Daily Living

In addition to exercise, T1DM patients' activities of daily living are crucial for reducing the development and progression of their disease and the risk of all-cause mortality (4, 25). Because many people with T1DM appear to have less hypoglycemic anxiety during their daily activities than for planned exercise, it may make sense for inactive people with T1DM to first try to increase their daily activities rather >

Table 3

Strategies to keep active insulin low during endurance exercise (30 minutes or longer) in individuals with T1DM (adapted from (21)). ^a=Even without automated insulin adjustment; ^b=Recommendation does not apply to ultra-long-acting insulin analogues (insulin degludec; insulin glargine U300) unless physical activities that last several days are planned. For the (less) long-acting insulin analogues (insulin glargine U100, insulin detemir), recommendations for basal insulin dose reductions are difficult to generalize and usually only useful for prolonged intensive activities.

INSULIN THERAPY	EXERCISE IN THE FASTED STATE	START OF EXERCISE WITHIN 2-3 H AFTER THE MEAL	START OF EXERCISE MORE THAN 3 H AFTER THE MEAL
MDI	Reduction of basal insulin by ~ 20% ^b	Reduction of bolus insulin by 25-75%	Carrying out the usual basal and bolus insulin administrations, consumption of additional carbohydrates according to glucose levels and individual response
CSII^a	Reduction of basal rate by 50-80% 90-120 minutes before exercise	Reduction of bolus insulin by 25-75%	Reduction of basal rate by 50-80% 90-120 minutes before exercise or interruption of insulin pump therapy at the start of exercise
AID system	Switch to exercise mode 90-120 minutes before exercising (this will result in an increase in the target value)	Reduction of bolus insulin by 25-75% and announcement of planned exercise already during the meal	Switch to exercise mode 90-120 minutes before exercising (this will result in an increase in the target value)

than to plan structured exercise sessions (2). More research is urgently needed on interrupting prolonged sitting times in people with T1DM and to determine the specific glucose management requirements of increased activity in everyday life (2).

Perspectives and Conclusions

In addition to sound scientific evidence, the individual clinical expertise of diabetes teams and sports therapists/ trainers, technological and pharmacological innovations, the individual experiences of athletes with T1DM must be taken into account.

Bi-hormonal systems that use glucagon in addition to insulin to reduce the risk of hypoglycemia or the amylin analogue pramlintide to reduce postprandial glucose excursions are currently being developed (30).

The continuously improving accuracy of the different measurement systems, optimized interoperability and connectivity, the development of multi-hormonal systems and intelligent algorithms for insulin dose determination using data from invasive and non-invasive measurements enable athletes with T1DM to achieve increasingly better and safer glucose control.

There is a research gap on the effects of increasing activities of daily living among people with T1DM and their relevance to glucose management requirements.

Conflict of Interest

The authors have no conflict of interest.

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