Review Article

Management of diabetes mellitus in children and adolescents: engaging in physical activity

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Abstract: Regular physical activity is an important component in the management of both type 1 and type 2 diabetes mellitus (T1DM and T2DM), as it has the potential to improve glycemic control, delay cardiovascular complications, and increase overall well-being. Unfortunately, many children and adolescents with diabetes do not partake in regular exercise and physical activity for multiple reasons. This review identifies the barriers to participation from the aspect of the patient, caregiver, and the healthcare provider. The management of physical activity of children and adolescents with diabetes mellitus is unique and requires an understanding of exercise physiology and how it differs in these children and adolescents from those without the condition. These individuals are at risk for important and potentially life threatening complications including, but not limited to, severe or delayed nocturnal hypoglycemia. It is essential to identify these risks as well as, monitor and manage adjustments to carbohydrate intake and insulin dosing through basal-bolus regimen or insulin pump adjustments appropriately before, during, and after the exercise activity. This review discusses these issues and also outlines differences in management between patients with T1DM and T2DM.

Keywords: Type 1 diabetes; type 2 diabetes; diabetes mellitus (DM); sports; physical activity

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Introduction

Physical activity has been universally recognized as an important component of a healthy lifestyle in all individuals and this includes children and adolescents with diabetes mellitus as well. In addition to benefits for physical health, participation in regular exercise has been shown to improve school performance, cognition, and enhance quality of life (1). The American Academy of Pediatrics (AAP) recommends that all children, including those with diabetes mellitus engage in at least 60 minutes of daily physical activity starting at 5 years of age (2). Exercise, insulin, and dietary management were described as three components important for management of blood glucose regulation by Joslin as early as the 1950s (3). Regular physical activity has been shown to improve cardiovascular complications (hypertension and dyslipidemia) and improve insulin sensitivity, leading to an improvement in glycemic control in these patients (4-6). Despite these well recognized benefits, multiple studies demonstrate that children and adolescents with diabetes are less active when compared to children without diabetes (7-9). There are multiple factors which lead to limitations of physical activity in these individuals, including, but not limited to concerns for altered glycemic control associated with activity, need for increased and closer monitoring,

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Table 1 Diagnostic criteria for diabetes mellitus and pre-diabetes

Diagnostic criteria for diabetes mellitus
HbA1c ≥6.5% or,
Fasting plasma glucose ≥126 mg/dL, or
2 hour plasma glucose ≥200 mg/dL during an Oral Glucose Tolerance Test, or
Random blood glucose ≥200 mg/dL associated with symptoms of hyperglycemia, or hyperglycemia crisis
Diagnostic criteria for pre-diabetes
HbA1c 5.7–6.4%, or
Fasting plasma glucose of 100–125 mg/dL, or
2 hour plasma glucose 140–199 mg/dL during an Oral Glucose Tolerance Test

and fear of being ostracized and feeling "different" while participating in sports with a chronic disease. It is important for families, friends, peers, coaches, and health care providers to identify and address these concerns early to limit sedentary behavior and promote physical activity in children and adolescents with diabetes mellitus.

Definitions and diagnostic criteria

Diabetes Mellitus is a disorder of glucose metabolism and is classified into multiple types based on underlying pathophysiology. The two most common types of diabetes are type 1 and type 2. Type 1 diabetes mellitus (T1DM) is characterized by an absolute deficiency of insulin, and is seen most often in children and adolescents, whereas type 2 diabetes mellitus (T2DM) is caused by insulin resistance, inadequate secretion of insulin and is generally associated with overweight and obesity. As per diagnostic criteria from the American Diabetes Association (ADA), the diagnosis of diabetes mellitus can be made in several ways as summarized in *Table 1* (10). It should be noted that unless there is a clear clinical diagnosis, a second confirmatory test is required. Individuals with prediabetes may be diagnosed similarly using criteria listed in *Table 1*.

Epidemiology

T1DM is the most common type of diabetes in children and adolescents with a prevalence of 20 to 25 per 100,000 in the United States (11). Over the last few decades, with increasing rates of obesity, the prevalence of T2DM has increased to approximately 12 per 100,000 (12). Individuals with T2DM are at a higher risk for developing complications early (13).

Physiology of exercise

An understanding of glucose metabolism and hormonal changes occurring during exercise is important for guiding appropriate management of glycemic control during participation in physical activity in these children and adolescents. The major sources of fuel for the body during exercise are fat and carbohydrates (14,15). Glucose is obtained from carbohydrates in the diet and is stored as glycogen in the liver and skeletal muscle during the resting state (15). Soon after exercise begins, muscle glycogenolysis serves as the primary source of glucose. At about 20–30 minutes into the physical activity, fatty acid breakdown contributes to the energy requirements needed for exercise. During prolonged exercise regimens and sports activities, the energy is derived primarily from free fatty acids (15).

The physiology of muscle contraction is complex and needs consideration as well. Briefly, exercise requires adenosine triphosphate (ATP) production, which occurs in balance with the various energy systems in the body, including the glycolytic pathway, phosphagen system, and aerobic mitochondrial respiration (15). During the initial few seconds of exercise or limited high intensity contractions, ATP is produced through reactions involving creatine kinase and adenylate kinase. Adenylate kinase leads to the production of adenosine monophosphate, which promotes glycolysis through the activation of phosphorylase and phosphofructokinase (15). Adenosine monophosphate production and increase in intracellular calcium and phosphate promote glucose uptake by muscles and glycogen breakdown (15).

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Insulin, glucagon, and other counter-regulatory hormones are responsible for maintaining glycemic control during aerobic exercise (15,16). Under normal circumstances, insulin is produced in response to hyperglycemia and acts by promoting glucose uptake by muscle and liver for purposes of metabolism, for storage as glycogen, and also for inhibition of fat and protein breakdown (ketogenesis) (15). Glucagon is released in response to exercise to provide energy by stimulating glycogenolysis and gluconeogenesis to prevent hypoglycemia and maintain homeostasis (15). The complex feedback interactions between insulin, glucagon, and other counter-regulatory hormones (catecholamines, growth hormone, cortisol) maintain a balance between glucose utilization and glucose production (3,16). Glucose metabolism by muscle is also highly regulated. Glucose is delivered to active muscle groups via increases in local blood flow, based on metabolic demand (14). Glucose uptake into muscle cells is then mediated by GLUT4 glucose transporters. GLUT4 gene expression is stimulated during exercise which increases glucose transport into the muscles, and this transport changes with insulin resistance (3,14,17). The mechanisms are complex, but believed to be via intracellular calcium release following muscle contraction (17).

Hormone responses also vary depending on exercise types. With mild to moderate aerobic exercise, glucagon secretion is increased and insulin secretion is decreased, so rate of glucose release is matched to the glucose uptake by muscles (6,16). This is in contrast to more intense exercise, where insulin release first decreases and then increases in opposition of the counter-regulatory hormones (16).

Physiology in type 1 diabetes

Patients with T1DM do not have the typical regulatory insulin response to hyperglycemia. They are therefore more prone to hypoglycemia or hyperglycemia associated with exercise and exogenous insulin administration. Glycemic control can become more predictable over time with regular physical activity and appropriate management of diabetes care during exercise. Individuals with T1DM may not have predictable or adequate endogenous glucose production due to multiple factors. There may be an increased risk of hypoglycemia due to lower glycogen stores, impaired glucagon secretion due to alpha cell dysfunction, and decreased glucagon sensitivity (18). Exercise causes increased blood flow to the muscles, leading to a more local glucose and insulin delivery, which also contributes to hypoglycemia. Exercise leads to mobilization of the glucose transporters which increases glucose uptake by the muscles (16). Patients with T1DM have increased rates of gluconeogenesis, which may help maintain blood glucose levels (18,19). Another difference to note between individuals without diabetes and T1DM patients during physical activity is that glucose production is primarily by glycogenolysis in the former versus gluconeogenesis in the latter (3). Studies have shown that a ten second sprint following physical activity lead to transient increases in counter-regulatory hormones, for which the risk of immediate hypoglycemia may be decreased, although this may not effect delayed hypoglycemia (3). When the amount of insulin in the system is not sufficient for the amount of exercise, or when the individual is exercising during illness, increased counter-regulatory hormone production can lead to hyperglycemia associated with ketone production (3). The presence of ketones can thus be used as an indicator of inadequate insulin effect. Hyperglycemia and ketosis should be monitored closely in the children who are not routinely well controlled and who start exercise, as the counter-regulatory response may be amplified. It has been shown that controlled (and uncomplicated) T1DM does not impair optimal athletic and physical performance (20) and children and adults with good control of diabetes have exercise capacity similar to matched controls (3,15,21). Anaerobic exercise or high intensity activity leads to increase in counter-regulatory hormones and hyperglycemia is expected almost immediately after start of exercise. This is often transient and can eventually lead to hypoglycemia a few hours later. In contrast, aerobic activity increases the risk of hypoglycemia during and after exercise. In general, the aerobic activities which have more muscle involvement have a greater risk of hypoglycemia (3). Resistance training is often associated with steady blood glucose levels, although hyperglycemia should be monitored for in some individuals (6).

Physiology in type 2 diabetes

At baseline, obese adolescents with T1DM or T2DM have decreased aerobic activity when compared to non-obese individuals (15,22). Adolescents with T2DM have impaired exercise capacity even when compared to obese controls without diabetes (23). Insulin resistance in T2DM has been thought to be related to a combination of excess lipid production and mitochondrial dysfunction (24,25). Obesity is associated with the presence of increased free

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fatty acids, which in turn leads to increased fat storage causing a decrease in insulin sensitivity. Excessive free fatty acid production also leads to an increase in reactive oxygen species, which affects mitochondrial function (24). The presence of reactive oxygen species also effects adequate insulin secretion from the beta-cells from the pancreas (24). Regular physical activity leads to an overall improvement in insulin sensitivity with a reduction in baseline insulin levels (26). Exercise capacity has been shown to improve with regular physical activity in children despite not having any changes in the body mass index (BMI) (26).

Hypoglycemia and hyperglycemia

Physical activity is associated with blood glucose fluctuations leading to hypoglycemia or hyperglycemia. Fear of hypoglycemia appears to be the most common reason to avoid exercise in children and adolescents. Therefore, addressing the appropriate management of insulin regimen and carbohydrate intake is important to avoid these fluctuations in glycemic control for safety and also for reassuring the child/adolescent and families (27,28). Severe hypoglycemia may be related to insulin-dependent and insulin-independent glucose uptake. Early hypoglycemia occurs immediately after exercise and late/delayed or nocturnal hypoglycemia may occur many hours after physical activity even overnight following periods of activity in the afternoon and evening. Delayed hypoglycemia is most often due to an increase in insulin sensitivity post-exercise. It may also be related to decrease in counter-regulatory response or lack of insulin adjustment prior to exercise (29). Close monitoring for glycemic control for sports participation requires increased blood glucose monitoring and this may become a barrier in sports participation. On the other hand, exercise-induced hyperglycemia can be seen due to an increased adrenal response either due to the nature of the physical activity or short intense bouts of anaerobic activity. Mismatch of insulin dose and carbohydrates may also result in hyperglycemia, either from under-insulinization or excessive food or carbohydrate intake prior to or during exercise.

Management of type 1 diabetes with exercise

Importance of a care plan

A proper approach to optimizing glycemic control in the exercise and peri-exercise period involves adequate blood glucose monitoring, timely carbohydrate supplementation and proper insulin adjustments. All of these can be addressed by the development of a comprehensive 'Diabetes Care Plan', which involves a team approach to the balancing of carbohydrate intake and insulin administration, in order to achieve stable glycemia during physical activity (or as close to it as possible) (30).

Pre-participation evaluation

It is recommended that children undergo a pre-participation evaluation to identify any risk factors and to decrease risk of medical harm to the individual. It also serves as a chance to provide anticipatory guidance (31). Patients with T1DM should have a similar comprehensive pre-participation evaluation prior to initiation of any new physical activity. Details of history should explore all aspects of an individual's medical history and should not simply focus on sports-related history. Both in youth with and without diabetes, the cardiovascular history and exam is one of the most important aspects of the pre-participation evaluation. Ensuring regular visits with their local pediatric endocrinologist and regular communication with the diabetes care team are important measures in improving glycemic control. Strategies to avoid exercise related hypoglycemia or hyperglycemia should be discussed, in addition to quarterly assessment of glycosylated Hemoglobin (HbA1c) and glycemic control. Special attention should be given to potential risks of microvascular complication precaution and related concerns including blood pressure and concerns for the presence of hypertension. Exercise may improve hypertension and should be encouraged. Individuals with more advanced complications such as proliferative retinopathy or neuropathy should avoid exercise and activities which can cause sudden increase in blood pressures (3,5). Recommendations for adequate foot care for all athletes should also be in place.

Blood glucose monitoring

Optimal blood glucose monitoring is essential to avoid acute complications related to exercise such as hypoglycemia and hyperglycemia with ketosis. It is recommended that blood glucose levels be checked prior to starting exercise, during, and after exercise. Prior to starting exercise, it is recommended that a patient's blood glucose be greater than 90 mg/dL (5). If initial blood glucose levels are low, the individual should avoid physical activity at that time and consume

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sufficient carbohydrates to achieve euglycemia (32). Exercise and physical activity should also be avoided if there is significant hyperglycemia with/without ketones present as this could induce diabetes ketoacidosis (DKA) (3,33). During periods of continuous physical activity, it is recommended that blood glucose levels be monitored about every 30 minutes, and then 15 minutes after completion of exercise, and at bedtime. In addition, more frequent monitoring may be needed over the next 24 hours due to increased risk of delayed hypoglycemia especially until the individual's glycemic response pattern to exercise is well defined (31,34). Optimal sports performance particularly in activities requiring the highest focus and precision would be expected when glycemic control is in a reasonably normal range as cognitive function and "mental efficiency" have been shown to be relatively lower during periods of hypoglycemia or significant hyperglycemia (35).

Other screenings

It is appropriate to make sure the individual is up to date on surveillance and screening for complications prior to participating in sports, to help identify and manage any complications if present. An individual with diabetes should have thyroid function studies soon after diagnosis and repeated every 1–2 years. Celiac disease screening should be done soon after diagnosis and repeated 2–5 years after diagnosis, or if concerning symptoms arise. Fasting lipid profile should be obtained after 10 years of age. In addition, nephropathy should be screened for with microalbuminuria once the individual has had diabetes for 5 years, and retinopathy and neuropathy after 10 years of age and after the individual has had diabetes for 3–5 years (10).

Adjustment of insulin regimen

Patients with T1DM may need individualization of recommendations based on the type, timing, and duration of physical activity the individual is participating in, with specific adjustments based on their treatment regimen. This will facilitate appropriate guidance for insulin dosing and carbohydrate ingestion. The management of diabetes during physical activity involves balancing of the type and timing of insulin given, the amount and timing of carbohydrate administration, fluid and electrolyte replacement, and management of complications including hypoglycemia, hyperglycemia, and ketones. Attention should be given to additional factors which may affect insulin dosing as well. For example, insulin absorption is increased in the exercising limb due to increased blood flow, and therefore it is recommended that individuals avoid injections in the exercising limb or muscle groups (3). Also, higher temperatures increase insulin absorption while cold weather decreases insulin absorption (3).

Basal-bolus regimen

The use of multiple-dose injections to address the insulin requirements in T1DM is the simplest, yet can be effective. Insulin requirements are covered generally by a once daily injection of long-acting "basal" insulin, in addition to several "short-acting" insulin bolus doses to cover food intake and hyperglycemia through the day. Adjustments of pre-meal short-acting insulin with a reduction of the bolus dose is effective in decreasing the risk of hypoglycemia associated with exercise (33). Adjustment of basal insulin dosing on the day prior to exercise should not be routinely done due to risk of hyperglycemia outside of the physical activity, but may be considered in certain circumstances such as camp (6).

Insulin pump (continuous subcutaneous insulin infusion)

Insulin pumps handle the daily insulin requirement by providing a continuous infusion of short-acting insulin at a low rate to provide the basal insulin requirements, along with bolus doses for the prandial requirements. Disposable Infusion "sets" or "pods" along with an insulin reservoir are changed every 2–3 days, and catheter tubing can then infuse into the subcutaneous space providing the insulin delivery. The use of insulin pumps may be associated with lower rates of early, severe, and delayed hypoglycemia if appropriate insulin rate adjustments are made (29). Early hypoglycemia can be prevented by suspending or decreasing the basal rate during exercise. The risk of nocturnal hypoglycemia can be reduced by decreasing or even suspending basal rate during exercise, followed by a temporary basal rate reduction of at least 20% for the next several hours or overnight (29). A common time for children and adolescents to exercise is after school, although this is often associated with nocturnal hypoglycemia, typically occurring between midnight and 2 AM. Although decreasing basal insulin during and after exercise does significantly decrease the number of hypoglycemic events, it is useful for patients/families to know that it does not eliminate the risk completely. However, hypoglycemia may be less severe and amenable

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to easy treatment. It is important to remember that there may be additional tendency towards hyperglycemic events as well (33,36). Hyperglycemia following exercise is more commonly associated with high intensity exercise due to increased catecholamine production (3). This may be prevented with a small bolus immediately after completion of the physical activity (3). Post-exercise bolus dosing should be done with caution due to possibility of severe nocturnal hypoglycemia, which has been associated with the fatal "dead-in-bed" syndrome (6,37). It is important to be aware of the types of activities that may lead to hyperglycemia instead of the more common occurrence of hypoglycemia as one learns about the individual's own unique glucose response during exercise.

Continuous glucose monitoring (CGM) technology

CGM offers closer monitoring and can help decrease glycemic excursions and prevent dangerous hypoglycemia or hyperglycemia by early warning, whether used along with multiple daily injections or insulin pumps. While persons using multiple-injection regimens can certainly still benefit from CGM, additional technology offers the pump users greater flexibility and added functionality. For example, CGM linked to an insulin pump (sometimes called Sensor-Augmented Pump therapy) is now available with automated algorithm processors to suspend basal insulin delivery automatically if blood glucose drops below specified set thresholds (sometimes called "low glucose threshold suspend"), and can be very effective in reducing hypoglycemia (38). Various strategies may be used to fine-tune insulin dosing to mitigate exercise-associated dysglycemia (39).

Approach to pre-exercise period

In the preparation phase for the sports activity/physical activity participation, it is recommended to have a well-balanced meal containing carbohydrates (CHO), protein and fat about 3–4 hours prior to exercise (40). At the same time, one should avoid exercise during peak insulin action. Additionally, in T1DM patients, about an hour prior to starting, about 1–2 grams of carbohydrates/kilogram body weight (g CHO/kg) consumption without insulin coverage should occur for longer duration planned activities (40). A pre-exercise blood glucose check is essential, as it can guide pre-exercise carbohydrate dosing and insulin dose adjustments. Pre-exercise blood glucose targets are generally recommended to be in the 90–250 mg/dL range (5). Below this threshold blood glucose of 90 mg/dL, a pre-exercise carbohydrate snack is recommended and intense physical activity should be avoided (39). Within this target range, exercise can be initiated, with regular consumption of carbohydrates depending on intensity and type of exercise and the amount of active insulin present. And if glucose levels are greater than 250 mg/dL, ketones should be checked and if present, exercise should be held, with conservative insulin correction given if significant hyperglycemia (39). Severe hypoglycemia, defined by blood glucose is less than 50 mg/dL or hypoglycemia requiring assistance, if within the previous 24 hours, should also be a relative contraindication to exercise (6). If the sports participant is in the euglycemic range noted above and no compensatory insulin adjustments have been made in the period before the activity, it is important to add a carbohydrate snack prior to starting physical activity to prevent risk of hypoglycemia. Adult guidelines have recommended consuming 10–15 gram of carbohydrates prior to starting exercise, although with children the amount of carbohydrates consumed depend greatly on blood glucose level prior to start of activity, duration and intensity of physical activity (36). Maintaining hydration is an extremely important factor in this broader context not directly related to insulin and carbohydrates. Adequate fluid intake should be maintained in the pre, intra, and post activity periods to prevent dehydration (6).

Approach during exercise

Regular monitoring of blood glucose should be performed, and carbohydrate and/or insulin doses be considered with the goal to maintain blood glucose in the 120–180 mg/dL range though an individualized approach is always best (20). For more strenuous and prolonged activities, additional carbohydrate supplementation is typically required to replete stores. The amount of carbohydrate intake should equal the amount of carbohydrates being consumed, or about 0.5–1.5 g CHO/kg for each hour of strenuous activity (5,40), and on the higher end of the range (1–1.5 g CHO/kg) if pre-exercise insulin doses have not been reduced.

Approach post-exercise

One should consider replacing carbohydrates immediately following exercise. Due to the delayed hypoglycemia effect,

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Table 2 Key points: exercise and safety

Have supplies ready to treat hypoglycemia and train any coaches and supervisors re: glucagon use in case of emergency
Check blood glucose often, including pre-exercise, during any prolonged physical activity and in the post-exercise period
Be aware of the common symptoms of hypoglycemia
Consider insulin adjustments as needed to prevent hyperglycemia, pre-, during, and post-exercise, based on type of planned activity
Be aware of the numerous factors that can influence *food effects on glucose levels*:
(I) Carbohydrate content
(II) Simple *vs.* complex (fast *vs.* slow acting)
(III) Protein and fat content
(IV) Timing of intake in relation to exercise
Be aware of the numerous factors that can influence *insulin effects on glucose levels*:
(I) Site of injection (avoid injecting into the exercising muscle groups)
(II) Ambient temperature (be cautious with extreme conditions)
(III) Timing of dose in relation to exercise
Baseline glycemic control helps promote optimal performance. This involves regular visits with pediatric endocrinology and HbA1c checks
Keep any coaches or training staff informed about the athlete's diabetes
Carry a medical alert tag or identification at all times denoting the diabetes status. Make sure emergency contact information is accessible to any coaches or supervisors
Other general safety advice regarding exercise and athletics:
(I) Adequate hydration
(II) Use the proper equipment and technique
(III) Use the "the buddy system"

blood glucose monitoring hourly and overnight (if the activity is in the afternoon or evening) is prudent. Changes in insulin sensitivity post-exercise is believed to be one of many mechanisms causing late or delayed hypoglycemia, and this effect is seen particularly following intermittent high-intensity exercising (10). Please refer to guidelines listed in *Table 2* for key points regarding exercise safety.

Exercise management in T2DM

Management of children and adolescents with T2DM is unique in that it combines behavioral, dietary, and physical activity components of an individual's lifestyle in addition to possible pharmaceutical interventions for appropriate management. There is also the added opportunity for managing individuals at risk for developing T2DM if they are identified early enough with a diagnosis of impaired glucose tolerance or pre-diabetes. Puberty is a time of relative physiologic reduction in insulin sensitivity and of the added behavioral component of physical inactivity which can both increase the risk of obesity and tendency towards developing T2DM (29). The optimal time to intervene in at-risk children is in childhood prior to starting of puberty. Studies have shown that lifestyle intervention has been associated with improved glycemic control in adolescents who have impaired glucose tolerance. Experimental studies support this, showing improved glycemic control along with improvement in fasting insulin levels (29,41,42). The management of exercise in patients with T2DM is focused primarily on behavioral aspects by establishing routines that promote regular physical activity and reduce sedentary activity. This may be particularly challenging in individuals and families with established sedentary and unhealthy lifestyles (3,29). It is recommended that patients with T2DM participate

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in at least 60 minutes of moderate to vigorous exercise daily (43).

The management of T2DM is typically healthy lifestyle modification, metformin, and in many cases insulin depending on the presentation and level of glycemia. There are other less commonly used drugs which are not FDA approved in the pediatric population.

Metformin is the first line pharmacologic agent used for T2DM in the pediatric population, and works by improving insulin sensitivity (43). Common side effects include abdominal discomfort and diarrhea, but can sometimes be mitigated by taking with food. Other medications commonly used in T2DM, but are not currently FDA approved for use in children, include sulfonylureas, thiazolidinediones, alpha-glucosidase inhibitors. If being used off-label, side effects should be closely monitored.

With presence of some residual beta cell function and insulin resistance and less effects on the counter-regulatory mechanisms (3), the risk of hypoglycemia is decreased in patients with T2DM. Despite this, insulin combined with physical activity may still lead to hypoglycemia and should be monitored closely for possible adjustments with insulin regimen, as elaborated in the discussion above.

Additional considerations

- Controlled and uncomplicated T1DM does not (and should not) impair optimal athletic and physical performance, so young people with T1DM should be strongly encouraged to pursue sports interests;
- *Fear of hypoglycemia* is very common and may drive many people with diabetes to keep blood glucoses higher than needed. Hypoglycemia is more troublesome in interfering with exercise and activities than is mild hyperglycemia, so strategies to mitigate hypoglycemia must be emphasized;
- While general targets and guidance can be provided (as described above), empirically derived and individualized goals and targets should always supersede any general "protocol".

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Footnote

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