DIABETES MELLITUS MANAGEMENT STRATEGIES IN ATHLETES

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Glycemic control is the biggest challenge for athletes with diabetes mellitus (DM) on insulin therapy. Done well, it can keep glycogen metabolism normal and allow performance improvement through adjustment of the insulin doses to the specifics of nutrition and exercising. In DM Type 1 and Type 2 patients, intense physical activity and resistance exercising, as well as interval training, enable optimal physiological adaptation during the training period and prove to be beneficial when the athlete does one-time exercise sets. But for athletes with DM on insulin therapy, keeping blood glucose at the optimal level is not the only important issue. It is also necessary to factor in the potential body temperature regulation disturbances that increase the risk of heat stress during training/competition, learn the effects the drugs used by athletes may have on the glycemic status, control electrolyte balance and dehydration, know how to execute the application for permission to use insulin for therapeutic purposes submitted to the anti-doping organization. The purpose of this review was to draw attention of sports medicine physicians and coaches to the above problems and to the need for wider use of the new DM control technology; help athletes with DM on insulin therapy continuously perform well and ensure their athletic longevity.

Keywords: athletes; diabetes mellitus; therapeutic use exemption; insulin; physiological adaptation, sports performance, physical loads/exercises

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СТРАТЕГИИ УПРАВЛЕНИЯ САХАРНЫМ ДИАБЕТОМ У СПОРТСМЕНОВ

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Контроль гликемии — самая сложная проблема для получающих инсулин спортсменов с сахарным диабетом (СД). При хорошем управлении гликемией обмен гликогена может быть нормальным, а работоспособность повышена коррекцией доз инсулина в соответствии с физической нагрузкой и питанием. Интенсивность физической нагрузки, упражнения с сопротивлением, интервальные тренировки при СД 1-го и 2-го типов обеспечивают оптимальную физиологическую адаптацию в период тренировок и демонстрируют хорошие гликемические преимущества при однократных нагрузочных сетах. Но для получающих инсулинотерапию спортсменов с СД важно не только поддержание оптимального уровня глюкозы во время тренировок и соревнований. Нужно учитывать и потенциальные нарушения терморегуляции, увеличивающие риск теплового стресса во время тренировок/соревнований, знать возможное влияние применяемых спортсменами лекарств на гликемию, электролитный баланс и дегидратацию, знать порядок оформления направляемых в антидопинговую организацию документов для запроса на терапевтическое использование инсулина. Целью обзора было попытаться привлечь внимание спортивных врачей и тренеров к вышеописанным проблемам и к необходимости более широкого использования новых технологий по контролю СД; помочь применяющим инсулин спортсменам с СД сохранять высокую работоспособность и спортивное долголетие.

Ключевые слова: спортсмены, сахарный диабет, разрешение на терапевтическое использование, инсулин, физиологическая адаптация, физические нагрузки/упражнения, спортивная результативность

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One of the problems faced by athletes with type 1 or type 2 DM (T1DM, T2DM) is reaching the maximum performance level when their blood glucose level deviates from the optimal value even minimally. Exercising is often more challenging for insulin users because their contracting muscles can stimulate absorption of the blood glucose regardless of the current insulin level, which leads to hypoglycemia. Moreover, even T2DM patients that do not use insulin on a daily basis need to balance many factors to ensure acceptable exercise tolerance. There is an extensive list of conditions that need to be observed in order to maintain the glycemic status optimal for sports (Fig. 1).

Thus, modifiable factors associated with exercising can cause significant fluctuations in the blood glucose level. In addition, insulin doses and nutrition should be adjusted to prevent hypo- or hyperglycemia both during and after the exercise session. Water and electrolyte balance, which can be disturbed by hyperglycemia and medications commonly prescribed to DM patients, is another factor potentially altering athletic performance.

Blood glucose control

Strong athletic performance requires keeping the blood glucose level within the safe range. Therefore, it is important to understand what factors can affect the blood glucose level and how deviations from the said range may change the athlete's current ability.

Hypoglycemia

When an athlete's blood glucose level drops below 4.0 mmol/l during a training session, he/she runs health deterioration risks, and if the level drops below 3.6 mmol/l, his/her training effectiveness goes down by approximately 20% [2]. Hypoglycemia is usually associated with the use of exogenous insulin; it often leads to peripheral hyperinsulinemia that develops during exercising. In addition to persistent hypoglycemia, which usually develops within 15 hours after the exercise session [3], there is an issue of the potassium level that may drop and remain low for several hours after blood glucose returns to the normal level [4]. The severity of hypokalemia can contribute to the development of a cardiac beat disorder and skeletal muscle contractility, which adversely affect athletic performance. Nocturnal hypoglycemia caused by training activities is another significant problem.

Hyperglycemia

Maintaining higher blood glucose level is an anti-hyperglycemia tactic often considered appropriate by athletes with DM on insulin therapy and sports medicine physicians. However, such tactic can make training less effective. When the blood glucose concentration is between 8.9 and 10 mmol/l, kidneys fail to completely reabsorb it from primary urine. When the above "renal threshold", which is unique to every person, is reached, glucose concentration in urine goes up, which results in a significant loss of fluid through osmotic diuresis. Besides, hyperglycemia bring down concentration of sodium, chloride and calcium in the blood plasma while increasing that of potassium [4], which weakens muscle function. In addition to the above, athletes with T1DM who have unexplained hyperglycemia (≥13.0 mmol/l) should mandatorily take a blood ketone test. If the test shows increased values thereof (≥1.5 mmol/l), training should be stopped because the level of both glucose and ketones can continue to rise even with moderately intense exercising in the background [5].

Types of exercise type and exercising time

Recently, strength training and high-intensity interval training (HIIT) have been attracting attention of the researchers as an alternative to long aerobic exercise sessions. Compared to such long aerobic exercise training sessions, intense physical loads, even in short sets, may be more beneficial from the points of view of general fitness and reduction of the cardiovascular disease risks, serum lipoprotein levels, endothelial dysfunction suppression [6]. Even in people with sedentary lifestyles and in elderly T2DM patients HIIT improves liver and muscle insulin sensitivity and their oxidative capacity better than long moderate-intensity exercising [6]. A study of physically active adults with T2DM showed that a single high-intensity interval training improves night and morning blood glucose within 24 hours after the training session [7]. T1DM patients may benefit from adding short HIIT sessions to their training schedules because they help decrease the risk of hypoglycemia during exercising. However, the question of whether HIIT sessions in the afternoon translate into greater risk of nocturnal hypoglycemia compared to aerobic exercise alone is still a matter of debate [8].

It should be noted that high-intensity exercise during training or competitions affect the release of catecholamines (adrenalin/noradrenalin) and can trigger significantly greater release of glucose from the liver, which, with exercising or competing in the background, potentially leads to hyperglycemia. In fact, the

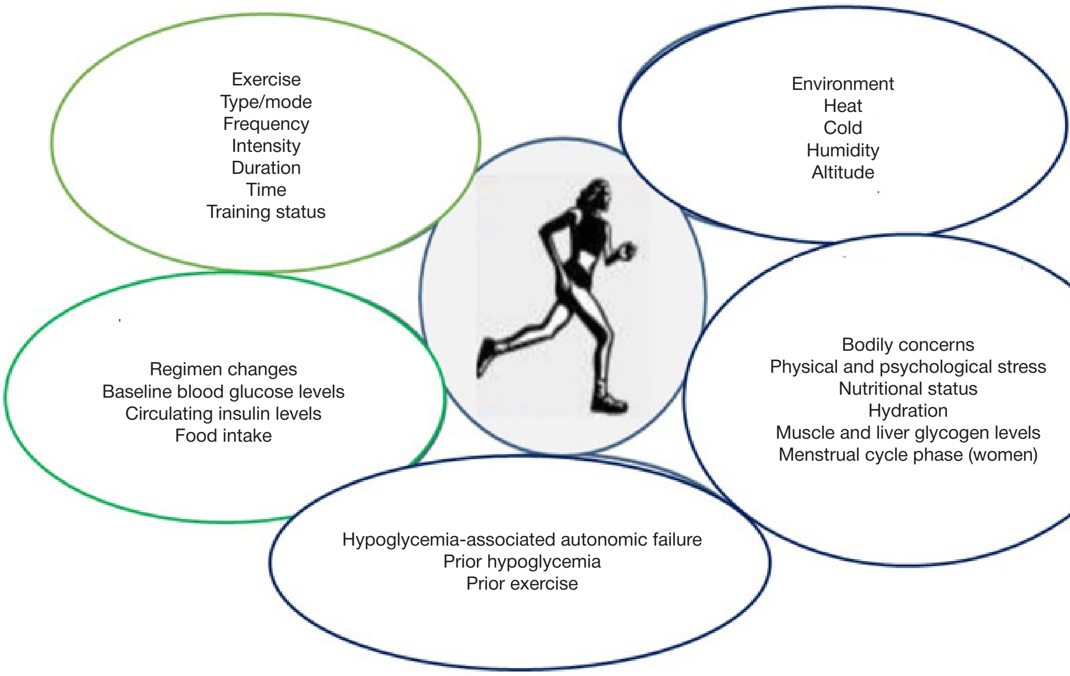

Fig. 1. Factors that can change blood glucose levels in T1DM patients during exercising [1]

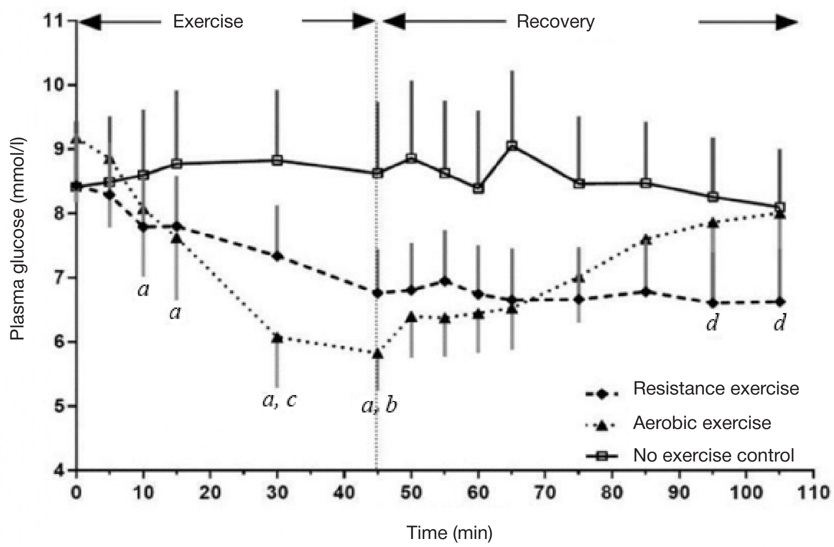

Fig. 2. Effect of different types of exercises on blood glucose stability in T1DM patients (HbA1c 7.1 ± 1.0%) [9]. Mean (± SE) plasma glucose level during exercising and over 60 minutes of recovery (*n* = 12). ◆ — no training (control); ◆ — resistance exercise (three sets of seven exercises, eight repetitions maximum, in 45 minutes); ▲ — aerobic exercise (running at 60% of the maximum calculated heart rate for 45 minutes); *a* — significant deviation from baseline for aerobic exercise; *b* — significant deviation from baseline for resistance exercise; *c* — significant difference between control and aerobic session; *d* — significant changes during recovery from aerobic exercise; the differences were considered significant only if they remained significant after Bonferroni adjustments

condition may develop even before the actual physical stress, since the anticipation of the event is a reason enough to force the catecholamine levels and blood glucose to go up [9].

Strength training exercises are also beneficial in many ways; it is advisable to include them in the training schedule of athletes with diabetes. In addition to boosting muscle performance by increasing intensity and rate of contraction, resistance exercises have other positive effects, including higher resting energy expenditure (faster basal metabolic rate), increased bone mineral density and improved body composition [10]. In adult T1DM patients, such exercises prevent blood glucose from excessive dropping better than aerobic training (Fig. 2) [11], and may even provide protection from such a drop if performed before aerobic exercises [12].

In a recent study, fasting exercise in people with T2DM resulted in a more significant improvement of postprandial glycemic profiles over the next 24 hours than exercising after breakfast [7].

In one study, 35 T1DM patients using insulin pumps exercised before breakfast on some days and in the afternoon on other; when they had fasting training sessions, they suffered less hypoglycemia events, and continuous glucose monitoring (CGM) readings were more likely to remain in the range close to the euglycemic state [3]. Other studies have shown that when T1DM patients do resistance exercises before breakfast their blood glucose level may grow up [8], and, on the contrary, when they exercised in the daytime, the blood glucose level went down [11]. Morning exercising can make blood glucose go up, which, to control hyperglycemia, is countered with an appropriate dose of rapid-acting insulin administered 2 hours after the session; this dose of rapid-acting insulin does not cause hypoglycemia [13]. Although the studies cited were small, their results, as limited in application as they are, suggest that athletes with T1DM who frequently suffer hypoglycemia may want to exercise in the morning, and those struggling with hyperglycemia may go for daytime sessions every now and then. The type and time of the forthcoming competition should be factored into the recommendations given to athletes with DM: anaerobic exercising in the daytime may yield better results in the short term, while regular training sessions in the morning may improve the performance when it is generally reduced [14].

Carbohydrate intake and insulin dose adjustments as basis for the athletic training optimization

Athletic competition requires prevention of both hypo- and hyperglycemia. In particular, non-prevented hypoglycemia will certainly reduce physical performance in training and in competitions [15], but glycemic balance can be achieved with the help of a strategy of correct carbohydrate intake, adjustment of insulin doses and time of their administration. Usually, hypoglycemia prevention when a training session lasts 30 minutes requires no additional carbohydrates or insulin dose reduction. Aerobic exercise lasting 30–60 minutes with low/normal insulin levels may call for 10–15 g of carbohydrates to prevent hypoglycemia [16]; if there is relative hyperinsulinemia in the background (after administration of bolus insulin, i.e., short (ultra-short) action insulin to maintain target blood glucose level after food intake and to control hyperglycemia), 30–60 g of carbohydrates per hour of exercise may be required [17]. For long training sessions or competition events (such as a marathon), this additional carbohydrate intake is beneficial regardless of the type of diabetes [18].

Table. Pre-meal insulin bolus injection reduction recommendations, applicable if training session starts within 90 minutes after bolus administration*

Type of activity	Duration of activity about 30 minutes	Duration of activity about 60 minutes
Light aerobic exercise (30–39% PR**)	–25%	–50%
Moderate intensity aerobic exercise (40–59% PR)	–50%	–75%
Intensive aerobic exercises (60–89% PR	–75%	Not rated

Note: * — compiled from sources [29, 30, 31, 32]; **PR — pulse reserve.

After exercising, the level of muscle glycogen restores rather slowly, at a rate of 5–7% per hour. The rate of recovery increases when the glycogen depot is depleted and slows down as it fills up. At the same time, as muscle glycogen level reaches the usual value, the effect of insulin begins to weaken [19]. On the positive side, the earlier glycogen level is restored, the lower the likelihood of an athlete with T1DM developing late-onset hypoglycemia, which occurs a day or two after training. Insufficient carbohydrate intake after exercising or taking carbohydrates when blood insulin is low can also reduce or delay glycogen recovery in the body. Therefore, to maintain and restore liver/muscle glycogen and blood glucose levels, athletes in training are advised to take a sufficient amount of carbohydrates before, during and after long exercising sessions (moderate or high intensity) appropriate to the adequate doses of insulin, especially during the "window of opportunity" (30 minutes to 2 hours after exercising).

Adjusting insulin doses to prevent hypoglycemia

As a substitute for, or in addition to, taking carbohydrates with the aim to mitigate the risk of exercise-induced hypoglycemia, both basal and/or bolus insulin can be reduced. People using multiple daily injections of insulin (intensified basal insulin therapy) can have the basal insulin doses administered both before and after the training session reduced by 20%. To optimize blood glucose levels during exercising, athletes can also adjust administration timing and size of the bolus [20] of rapid-acting insulin taken with meals and pre-session snacks. Such adjustments, not changing the blood ketone level significantly, are feasible when an exercising session lasts for up to 45 minutes continuously [21]. Athletes using an insulin pump, which enables continuous subcutaneous insulin infusion, can make the decrease of the blood glucose level less abrupt by reducing or pausing basal insulin infusion at the beginning of a training session or even 30–60 minutes before it [22]. If the session takes place within 2–3 hours after a bolus injection (done with pen or pump), the 25–75% drop of the insulin level (before meals) may diminish the likelihood of hypoglycemia [23] (Table). Regardless of whether insulin dosage has been altered or not, frequent blood glucose checks and possibly intake of additional carbohydrates may be required to ensure safety of an exercising athlete.

For those receiving injectable insulin (pens), the risk of nocturnal hypoglycemia can be minimized by reducing the daily basal insulin dose by approximately 20% and reducing the prandial bolus insulin and intake of low-glycemic carbohydrate food after evening training sessions [24]. Patients with an insulin pump can avoid nocturnal hypoglycemia by reducing the basal injection rate by 20% for sleep time and for the period of 6 hours after daytime exercising [25]. For T1DM and T2DM patients on insulin therapy, it may make sense to have an additional snack before bedtime (2 bread units, 20–24 g of carbohydrates), check the glucose level at night and/or use a signaling CGM system [26].

It is also important to note that the rate of absorption of insulin can be improved by heating the injection point or massaging it or the area around it, with such improved absorption translating into shorter injection-to-action time [27].

There are other ways, alternative to insulin dose and carbohydrate intake adjustment, to prevent hypoglycemia, at least in the short term, like a short maximum effort sprint before or after a session of moderate intensity exercise [28].

Insulin therapeutic use exemption

The athlete taking insulin and the doctor prescribing the drug must comply with the requirements of the Russian national anti-doping rules and those by international anti-doping organizations, since insulin is included in the S4 class "Hormones and metabolic modulators" of the Prohibited List. Athletes requiring insulin must apply to the anti-doping organization and obtain the appropriate therapeutic use exemption. Medical documents attached to the application should be prepared by the physician prescribing the insulin. These documents, under the requirements of the WADA International Standard for Therapeutic Use Exemptions [33], must specify that:

1) the prohibited substance or prohibited method in question is needed to treat a diagnosed medical condition supported by relevant clinical evidence;

2) the therapeutic use of the prohibited substance or prohibited method will not, on the balance of probabilities, produce any additional enhancement of performance beyond what might be anticipated by a return to the athlete's normal state of health following the treatment of the medical condition;

3) the prohibited substance or prohibited method is an indicated treatment for the medical condition, and there is no reasonable permitted therapeutic alternative.

Requirements for the preparation of medical documents for therapeutic insulin use exemption application are set out in the Therapeutic Use Exemptions Physician Guidelines: Diabetes Mellitus published to the Therapeutic Use Exemption section of the World Anti-Doping Agency's website and, in Russian, to the RUSADA Russian Anti-Doping Agency's website [34].

Oral hypoglycemic agents are not prohibited; they can be used without applying for a therapeutic use exemption (TUE).

Use of the new technologies

A breakthrough in DM control occurred in 1998, when continuous glycemic monitoring (CGM) system became widely and routinely used. Such systems measure glucose in the interstitial fluid continuously, every 5–15 minutes, relying on subcutaneous sensors, and transmit data to a smartphone/computer of the athlete, coach, sports medicine physician. However, there is a difference between the displayed interstitial glucose and its real level in capillary blood: on average, the data from the sensors arrives with a 8–10 minute delay (maximum — 20 minute delay). Thus, if the blood glucose level is stable, the readings will be close to the capillary glucose level, but during rapid glycemic changes the displayed value will be either lower or higher than the current real level.

Use of CGM systems by athletes is still a matter of debate. One study showed that such systems help detect asymptomatic hypoglycemia and hyperglycemia after exercise sessions (other studies identified accuracy limitations peculiar to the current systems and its dependency on the length of use of the sensor, irritation of the skin and problems with the contact therewith) [35]. Several studies have confirmed that CGM systems are accurate enough to be used in training session situations [36]; other researchers, however, reported insufficient accuracy and problems related to broken sensory filaments, inability to calibrate the systems and time from the moment the capillary blood glucose level changes to the moment it is reported by the sensor [37]. Although continuous monitoring is a very useful tool for tracking blood glucose trends during exercising and preventing hypoglycemia after the sessions, so far CGM systems cannot completely replace capillary blood glucose testing with individual glucometers.

Insulin pumps enable continuous subcutaneous infusion of insulin with continuous glucose monitoring in real time. Compared to daily basal-bolus injections, such pumps allow changing the basal insulin delivered subcutaneously during training, which makes stress response more physiological. Bodies of people using a pen once or twice a day to administer basal insulin are less quick to respond to the changing demand therefor during and after exercising [38]. However, athletes must be able to control the pump if it remains on during physical activity, and this can be difficult in contact sports, team games etc. Besides, environmental factors (such as heat) can adversely affect the quality of insulin in the pump.

Automated insulin delivery systems (closed loop type), called "artificial pancreas", are the state-of-the-art technology designed to treat insulin-dependent diabetes mellitus. Such systems include a CGM module, an insulin pump and control algorithms (some of which may be smartphone-based). It is a closed-loop system that, unlike a single CGM sensor, does not require the user to enter his/her data in response to the readings; the monitoring and insulin pump system automatically delivers the correct amount of insulin based on the values transmitted. Thus, the insulin infusion adjustment can be as accurate as the measuring device the whole system relies on [39]. Studies that involved T1DM patients showed that adding an alarm to the closed-loop system that is triggered when the glucose level falls below a predetermined critical level (4–4.5 mmol/l) reduces the risk of hypoglycemia during and immediately after exercising even further [40].

Other factors affecting the performance of an athlete with diabetes

Studies have shown that T1DM and T2DM patients often have thermoregulation disorders [41]. In particular, type 1 diabetes impairs perspiration, especially with higher level exercising in the background. Where dehydration can lead to further deterioration of sweating, it is very important to closely monitor blood glucose levels during competition in hot weather to avoid further exacerbation of the existing disorders body cooling mechanisms [42].

Studies that involved people with T2DM showed that increased sitting time is associated with poor glycemic control and metabolic risks, and that there is no dependency on the intermittent moderate to high-level vigorous activity [43]. Another study found that as little as 3 minutes of light walking combined with simple resistance exercises every 30 minutes of a period a person needs to remain seated for a long time enabled adequate glycemic management throughout the day [44].

The effect of drugs should also be factored in. In addition to insulin, all athletes with diabetes can take a variety of prescription or over-the-counter medications to treat a variety of diseases (conditions). Their potential impact on athletic performance will be largely mediated by the changes in blood glucose levels and fluid and electrolyte balance, which can impair hydration status and muscle contractility. Such medications are some antihypertensive, diuretic, steroid and non-steroidal anti-inflammatory drugs, symptomatic cold medications and some other substances.

Corticosteroids, which can be prescribed for some common conditions (e.g., asthma, arthritis, and allergic rhinitis), can cause hyperglycemia in people with diabetes [45]; these drugs also require a TUE. Antipsychotic drugs can reduce insulin sensitivity and thus increase the risk of hyperglycemia and dehydration in athletes with diabetes [46]. Medicines with phenylephrine or pseudoephedrine as active ingredients (e.g., cold/flu and allergy drugs) tend to increase glycogenolysis in the liver, same as catecholamines, which often leads to hyperglycemia in people with diabetes [47]. Of course, it is unlikely that athletes will use such drugs during competition: pseudoephedrine and adrenaline are on the WADA Prohibited List, and phenylephrine is in the Monitoring Program, but it is possible that younger and/or less experienced athletes can use them out of competition, not knowing the impact of these substances on athletic performance and blood glucose levels.

Athletes with T2DM can receive a therapy that combines insulin administration (basal insulin/mixed insulin/basal-bolus therapy) and oral glucose-lowering drugs. In these cases, special attention should be paid to the possible side effects of the patter that can disturb the electrolyte balance and influence athletic performance.

Metformin, one of the most well-known biguanide oral antidiabetic drugs, can cause indigestion and diarrhea. Another hypoglycemic agent, acarbose (an alpha-glucosidase inhibitor), produces a similar effect: it inhibits digestion and absorption of carbohydrates in the small intestine. Diarrhea can decrease the blood potassium level, therefore, athletes taking the above drugs should monitor their electrolyte levels more often, especially during the competition period.

Modern antidiabetic drugs such as glucagon-like peptide-1 receptor agonists (GLP-1 receptor agonists, or incretin mimetics), dipeptidyl peptidase 4 inhibitors (DPP-4 inhibitors, or gliptins), activate incretin response, reduce the level of postprandial glycemia by stimulating glucose-dependent secretion of insulin and inhibiting release of glucagon. The more common side effects thereof are diarrhea and vomiting, while dehydration is infrequent, which requires closer monitoring of the level of blood electrolytes in athletes. The use of GLP-1 receptor agonists was associated with the risk of acute pancreatitis, and a combination with insulin translated into an increased risk of hypoglycemia. Inhibitors of the sodium-dependent glucose cotransporter type 2 (SGLT2 inhibitors, or gdiflozins), as well as type 2 and 1 (SGLT1 and SGLT2) reduce renal glucose reabsorption and thus bring down blood glucose and glycated hemoglobin (HbA1c). Their positive side effects are the decreased body weight, systolic blood pressure and blood uric acid level. These drugs, increasing the volume of excreted urine (especially with initial hyperglycemia in the background), may lead to dehydration and side reactions associated with decreased volume of intercellular fluid: hypotension, postural dizziness, orthostatic hypotension. With some drugs of this class (canagliflozin), there was a slight but significant decrease in the total BMD of the hip joint, an increase in biomarkers of bone formation and resorption and a higher risk of bone fracture identifiable as early as 12 weeks into the therapy [48]. A medicine from this class, sotagliflozin (SGLT1 and SGLT2 inhibitor), has been approved for treatment of type 1 diabetes.

Since hypertension is a common complication of diabetes, it is possible that athletes with diabetes, depending on their age and history, may be prescribed angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor antagonists (ARA) or some diuretic drugs. ACE and ARA can cause hyperkalemia [49], and high blood potassium levels can impair athletic performance by making muscles weaker or cause cardiac arrhythmias that can even be fatal. Diuretics prescribed to control blood pressure lead to polyuria and increase the risk of dehydration and electrolyte imbalance. In particular, thiazide diuretics are associated with a greater risk of hyponatremia, which increases with age, is higher in women, and tends to affect people with lower weight more than those with higher weight. Thiazides can also increase urinary potassium loss, sometimes increasing the risk of hypokalemia [50]. In addition, the use of diuretics is regulated by the WADA standards.

CONCLUSION

Although glycemic management in athletes with diabetes can be quite challenging due to the intensity of exercising and hectic training and competition schedules, such athletes have the potential to be as successful as athletes without diabetes. The intensity, type and timing of exercising, as well as insulin and food dosage and timing, affect the athlete's blood glucose level and performance, but they can be effectively controlled with appropriate changes in the regimen. Athletes, sports medicine physicians and coaches need to be aware of the effects of blood glucose and medications on hydration and electrolyte balance in order to make the necessary adjustments seeking to achieve the optimal results. The latest technologies for diabetes monitoring and control, although somewhat limited in accuracy and use at present, can help athletes to better control glycemia and achieve peak athletic performance.

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