Hyperglycemic Emergencies in Athletes

Michael E. Chansky, MD\textsuperscript{a,b,*}, Jillian G. Corbett, MD\textsuperscript{b,c}, Evan Cohen, MD\textsuperscript{b}

**KEYWORDS**
- Diabetes
- Exercise
- Hyperglycemia
- Ketoacidosis
- Athletes

**EPIDEMIOLOGY**

Diabetes mellitus (DM) is a chronic endocrine disorder characterized by increased circulating blood levels of glucose and abnormalities in fat, protein, and carbohydrate metabolism, which can lead to longstanding macro- and microvascular complications.\textsuperscript{1} According to the Centers for Disease Control and Prevention statistics, it is estimated that 23.6 million people, or 7.8\% of the US population, are affected by DM. Among this group, roughly 185,000 are younger than 20 years of age, and 7.8 million are aged 20 to 39 years. This age group constitutes the majority of athletes and, thus, the population of interest for this discussion.\textsuperscript{2}

**TYPE 1 VERSUS TYPE 2 DIABETES MELLITUS**

DM is classified into 2 major groups, type 1 and type 2. Type 1 DM (formerly known as insulin-dependent diabetes mellitus (IDDM) or juvenile-onset DM) is caused by autoimmune destruction of pancreatic islet \(\beta\) cells, leading to loss of insulin secretion and absolute insulin deficiency.\textsuperscript{1} As a result, lifelong insulin replacement therapy is required for survival.\textsuperscript{3} Type 1 DM is the most common form of the disease seen in children and adolescents, particularly of European origin.\textsuperscript{1} As a result, the majority of athletic encounters will involve individuals with type 1 diabetes. When symptomatic, type 1 DM usually manifests with rapid onset of acute symptoms, the most severe acute complication being diabetic ketoacidosis (DKA).

Type 2 DM, the most common form of the disease (formerly referred to as non-insulin-dependent DM or adult-onset DM) is characterized by relative, rather than...
absolute, insulin deficiency.\textsuperscript{3} Patients suffer from a combination of inadequate insulin secretion and resistance to insulin action, which may eventually lead to β cell failure and need for insulin supplementation.\textsuperscript{4} Type 2 DM has a stronger genetic predisposition and is usually a disease of adulthood and obesity. The prevalence of type 2 DM is rising, specifically in children and teenagers.\textsuperscript{3} Symptoms are typically less acute in onset than those of type 1 DM, and patients are less prone to ketosis but rather a hyperosmolar, hyperglycemic nonketotic syndrome.\textsuperscript{4}

**DIABETES AND EXERCISE**

As previously noted, the prevalence of type 1 diabetes among children, adolescents, and young adults means this is the form of disease encountered in most athletes.\textsuperscript{5} This discussion focuses on the management of hyperglycemic emergencies in the athlete with insulin-dependent diabetes. A review of the body’s metabolic response to exercise and the physiologic effects of exercise in athletes with diabetes is important to understand the pathogenesis and therapy of DKA.

In any athlete, the primary goal during exercise is to maintain a supply of metabolic fuels for muscle and overall increasing energy needs.\textsuperscript{6} To achieve this during states of physical activity, the body undergoes specific changes to balance glucose use by muscle and the mobilization of fuel sources from other tissues. The primary sources of fuel during exercise are divided into those present in muscle and those from extra-muscular sources. Muscle sources include glycogen and triglycerides, whereas extra-muscular sources include glucose released into the bloodstream via glycogenolysis and fatty acids released from adipose tissue.\textsuperscript{7} During initial stages of exercise, muscle glycogen is used as the primary source of energy via anaerobic metabolism. As exercise duration increases, aerobic metabolism predominates, and energy is mainly derived via gluconeogenesis by the liver and release of free fatty acids.\textsuperscript{6} This aforementioned process is regulated by a complex neural and hormonal response at exercise onset, ultimately resulting in increased plasma levels of epinephrine, decreased levels of insulin, and increased levels of glucagon, cortisol, and growth hormone (counter-regulatory hormones). Epinephrine stimulates the release of free fatty acids from lipocytes and stimulates liver glycogenolysis. A decrease in insulin secretion and increase in the counter-regulatory hormones further stimulate lipolysis and increase hepatic glucose production.\textsuperscript{7}

In contrast to the organized process described above, the exercise response in a type 1 diabetic athlete is complicated, because normal endogenous variations in insulin and counter-regulatory hormones are absent. Instead, glucose homeostasis requires exogenous insulin administration, posing the challenge to maintain a balance between glucose level and insulin availability.\textsuperscript{6} During exercise, diabetics may experience problems with both excessive versus insufficient amounts of insulin, leading to either a hypoglycemic or hyperglycemic state.\textsuperscript{5} Hypoglycemia is a more frequently encountered problem and is usually a result of overinsulinization for various reasons. First, subcutaneously injected insulin is absorbed at a more rapid rate during exercise due to the increase in body temperature and skeletal muscle blood flow. In addition, the diabetic athlete does not have the ability to mount the normal hormonal response to exercise. This inability to decrease plasma insulin levels and increase secretion of counter-regulatory hormones causes a relative hyperinsulinemia, which impairs hepatic glucose production and worsens hypoglycemia.\textsuperscript{8}

More important to this discussion is the risk of hyperglycemia in the exercising diabetic. In the normal athlete, the body responds to exercise by suppressing insulin release and stimulating release of glucagon, leading to a synergistic increase in
plasma glucose levels. At rest, insulin is secreted and counter-regulatory hormone levels decrease, returning plasma glucose levels to normal. In type 1 diabetics, plasma glucose levels remain elevated following periods of exercise, since there is no rise in insulin level. This absence of insulin response impairs glucose uptake and stimulates hepatic glucose production, lipolysis, and ketogenesis, ultimately resulting in a hyperglycemic state and, in the most severe cases, ketoacidosis. Hyperglycemia with and without ketosis as well as the recognition, treatment, and prevention of both conditions are discussed in further detail below.

ACUTE HYPERGLYCEMIA AND KETOACIDOSIS

Acute hyperglycemia with or without ketosis is a potential hazard for any athlete with type 1 DM. In the absence of exercise, the most common precipitating factors for these conditions include inappropriate/inadequate insulin administration or infection. In addition to the heightened risk due to lack of insulin as described here, the diabetic athlete is prone to elevated serum glucose levels and/or ketone production for several other reasons. Exercise alone, especially in athletes with baseline poor glucose control or elevated levels before activity, can cause an additional increase in serum glucose. Since insulin is not available to promote glucose uptake peripherally, the body responds by releasing counter-regulatory hormones, which cause an even greater rise in serum glucose levels. At levels of extreme intensity, even in well-controlled diabetics, rising serum catecholamines exaggerate this response as well as promote free fatty acid and ketone body production, which can lead to DKA. Under most circumstances, this is a transient response, and within 1 hour, hormone levels and serum glucose return to normal. In poorly controlled diabetic athletes, however, this response is prolonged, and individuals remain in a hyperglycemic state for extended periods of time, which may predispose them to ketoacidosis. Finally, the anticipatory stress of athletic competition, even before activity begins, causes a rise in counter-regulatory hormone release, leading to elevated blood glucose before physical activity, thus predisposing to hyperglycemia and ketosis.

DKA is the most severe acute complication of hyperglycemia. DKA represents the body’s response to cellular starvation in the setting of insulin deficiency and counter-regulatory (primarily glucagon) hormone excess. Under normal circumstances, insulin is responsible for the metabolism and storage of carbohydrates, fat, and protein. It exerts its actions on 3 major organs: liver, adipose tissue, and skeletal muscle. In the liver, insulin causes glucose uptake and conversion to glycogen stores, while inhibiting glycogen breakdown. In adipose tissue, insulin stimulates triglyceride production from free fatty acids and glycerol, and inhibits their breakdown. In skeletal muscle, it promotes the incorporation of amino acids into protein, while preventing amino acid release from both muscle and hepatic protein sources.

In an insulin-deficient state, the body is unable to use glucose as fuel despite an elevated intravascular glucose level. The body responds by secreting counter-regulatory hormones (glucagon, catecholamines, cortisol, and growth hormone), precipitating a catabolic state. This leads to the breakdown of both protein and adipose stores as a potential source of intracellular fuel. Released free fatty acids are transported to the liver and converted to ketone bodies, primarily β-hydroxybutyric acid and acetoacetic acid. This process is further exaggerated in the setting of decreased hepatic glycogen stores. Without insulin, the body is unable to use these formed ketone bodies as an energy source. The end result is hyperglycemia, osmotic diuresis, and worsening ketonemia, leading to an anion-gap metabolic acidosis and DKA.
The classic clinical presentation of a patient in DKA includes a history of polydipsia, polyuria, dehydration, weight loss, generalized weakness, nausea/vomiting, and abdominal pain. Physical findings can include any of the following: tachycardia, hypotension, Kussmaul respirations (deep, rapid respirations), fruity odor on breath (secondary to acetone formation), poor skin turgor, altered mental status, and hypothermia. Hyperglycemia leads to an osmotic diuresis and volume loss, as well as profound renal-mediated electrolyte losses of sodium, potassium, chloride, phosphorous, calcium, and magnesium. In the early stages of the disease, patients may increase their fluid intake to compensate for these losses. However, as acidemia and ketosis progress, prostaglandins are released, causing peripheral vasodilation. Nausea and vomiting also occur, most likely as a maladaptive response to diminish acid load. Both responses, combined with continued diuresis, only contribute to a further state of overall volume and total body potassium depletion.

Laboratory findings in DKA typically consist of the triad of hyperglycemia, ketonemia, and metabolic acidosis, combined with varying electrolyte abnormalities. Patients usually present with serum glucose levels greater than 300 mg/dL, although lower initial levels may be seen in self-well-hydrated patients. Accumulation of ketoadcids leads to acidemia and ketonuria, and the resultant anion-gap metabolic acidosis. The anion gap is calculated by subtracting the sum of the serum bicarbonate and...
chloride concentration from the measured serum sodium concentration [Na⁺ - (Cl⁻ + HCO₃⁻)], with 6 to 12 mEq/L considered normal. An elevated anion gap may be the only clue to the presence of an underlying metabolic acidosis, and cannot be overlooked. Patients may also present with various electrolyte derangements. Patients typically present with pseudohyponatremia (caused by hyperglycemia and hyperlipidemia), and serum concentrations of potassium, magnesium, and phosphate may not accurately reflect the degree of total body deficit. Serum sodium is typically depressed 2.4 mEq/dL for every 100 mg/dL elevation of serum glucose over 100 mg/dL, particularly with serum glucose levels greater than 400 mg/dL.

TREATMENT

Because of the potential lethality and complications of untreated DKA, any athlete suspected to have DKA must be transported and treated in an emergency department setting. Patients should be placed on a monitor during transport and have at least one large-bore (16–18 gauge) intravenous line of normal saline (NS) running, as aggressive fluid therapy is the cornerstone of treatment. Once in the hospital setting, a rapid bedside glucose determination, a urine dip for ketones, and an electrocardiogram should be performed. A venous blood gas should also be considered in critically ill patients, to quickly obtain pH (approximately 0.03 lower than arterial pH), pCO₂, and important electrolyte levels, specifically potassium. In addition, a complete blood count, chemistry panel (including magnesium, phosphate, and calcium and determination of anion gap), and urinalysis should be obtained (Fig. 2). The goals of therapy include safe hydration and volume repletion along with correcting total body potassium deficiencies, metabolic acidosis, hyperglycemia, and other electrolyte disturbances at the approximate rate of occurrence. Meeting these goals safely involves carefully monitoring vital signs, electrolytes, anion gap, volume input/output, and insulin requirements until recovery is established. It should be noted that correction of hyperglycemia alone is NOT the end point of treatment, as normalization of the anion gap indicates resolution of the metabolic acidosis in DKA. The precipitating etiology of DKA should also be explored, including searching for an infectious source if indicated.

As stated above, rapid administration of intravenous fluids is the most critical step in the initial treatment of DKA. Hydration with isotonic saline will help to restore vital organ perfusion and improve renal clearance of glucose. Fluid deficit in affected adult patients averages between 5 and 10 L. The choice of fluid replacement has not been well established, but it is generally recommended to begin with NS, which may prevent a rapid fall in extracellular osmolarity and thus a transfer of free water into the central nervous system, one theoretical etiology of cerebral edema. After initial fluid replacement has begun, alternating with 0.5 NS or using 2 separate intravenous lines with normal and 0.5 NS has been advocated. A guideline for the rate of fluid replacement is 2 L within the first 2 hours, 2 L within the next 4 hours, and then 2 L in hours 6 through 12. Intravenous fluids should be changed to D5 0.5 NS once blood glucose levels approach 300 mg/dL, to prevent hypoglycemia. Although beyond the scope of this review, the particularly young athlete with new-onset diabetes and DKA may be at increased risk for cerebral edema, and fluid management should be adjusted according to pediatric critical care guidelines.

Supplemental insulin can be administered once initial laboratory data have returned, specifically determination of serum potassium concentration. On presentation, the vast majority of patients have initial potassium levels greater than 3.3 mEq/dL, secondary to acidosis and volume depletion, despite profound total body deficits.
The potential danger of initiating insulin therapy with low initial serum potassium is an intracellular shift, resulting in profound hypokalemia. If initial potassium is below 3.3 mEq/dL, insulin should be held, and an oral dose of 40 mEq of potassium should be given 15 to 30 minutes before insulin therapy or documentation of serum potassium concentration greater than 3.3 mEq/dL. Intravenous potassium supplementation (10–15 mEq/h in a monitored setting) should be reserved for the vomiting patient.
Potassium levels between 3.3 and 5.0 mEq/dL should prompt a minimum of 10 mEq/h replacement intravenously, in addition to simultaneous insulin therapy. Potassium levels greater than 5.0 mEq/dL should prompt insulin therapy alone, with careful attention to hourly monitoring of potassium, as therapy with fluids and insulin will predictably lower serum potassium concentration acutely.

Insulin replacement should be in a controlled manner as a continuous infusion, as boluses are thought to be less physiologic and no longer accepted as standard, especially in children and adolescents. The initial infusion dose should be 0.1 U/kg/h. Subcutaneous and intramuscular injections are not recommended, as absorption will be erratic in an ill and volume-depleted patient. A poor response to initial infusion rates should lead to increasing dosages by doubling the infusion rate. Therapy should be continued until the anion gap has closed. A common method of objective disease progression is to check hourly finger stick glucose and every other hourly serum chemistries.

Careful attention must be paid to other electrolytes such as phosphate, magnesium, and bicarbonate. Phosphate should be replaced as needed and done so via oral route, unless severe or symptomatic (rare) hypophosphatemia (below 1.0 mg/dL) is present. Failure to replenish phosphate can rarely lead to hypoxia, rhabdomyolysis, hemolysis, respiratory failure, and cardiac dysfunction. Complications of hypomagnesemia are also rare, and magnesium replacement can generally be accomplished by oral replacement. Finally, bicarbonate therapy is a controversial issue and is not routinely recommended. Advocates argue that therapy may improve myocardial contractility, elevate ventricular fibrillation threshold, improve catecholamine tissue response, and decrease work of breathing. The disadvantages may include, but are not limited to, worsening hypokalemia, paradoxic central nervous system acidosis and intracellular acidosis, sodium overload, and precipitation of cerebral edema. To date not a single randomized study has demonstrated any benefit to the administration of bicarbonate in DKA, and patients routinely recover from a very low initial pH with appropriate therapy.

The vast majority of athletes presenting with DKA are admitted to a monitored bed with experience handling continuous insulin infusions or a critical care setting. A minority of patients with mild forms of the disease (anion gap less than 18 mEq/L, glucose less than 300 mg/dL) may be managed in the emergency department for several hours and discharged with appropriate close follow-up.

PREVENTION PLAN

The most effective strategy of the discussed diabetic emergencies is prevention. Prevention strategy is multidisciplinary and involves educating the patient, parents, athletic trainers, and primary care doctor and involving an endocrinologist. Pillars of avoiding disaster include having a preparticipation physical examination, diabetes care plan, recognition education, and treatment education.

Preparticipation physical examination should assess hemoglobin A1c (HbA1c) quarterly to gain a general idea of the patient’s diabetic management. HbA1c of 7% or less is recommended by the American Diabetic Association for adults and of less than 7.5% for teens and adolescents, with 7% correlating with an average blood glucose level of approximately 150 mg/dL. The American Association of Clinical Endocrinologists has tighter recommendations for glycemic control, and individual goals should be discussed with the patient’s medical team. These levels serve as an overall measurement of an individual’s glycemic control over a 3-month period and not day-to-day variations.
Other aspects of the pre-participation physical examination in a young diabetic should include ophthalmologic examinations annually beginning 3 to 5 years after diagnosis, to screen for retinopathy, glaucoma, and cataracts. Diabetic nephropathy screening should take place 5 years after diagnosis by urine analysis for protein, and neuropathy screening, 5 years after diagnosis is made and annually thereafter. Neuropathy may affect tactile sensation and reflexes and be especially important in weight-bearing athletes, those with tight shoes, frequent blisters, or who walk barefoot. Less recognized effects of diabetic neuropathy include autonomic neuropathy, which may blunt the patient’s ability to recognize hypoglycemia or cause exercise intolerance or orthostatic hypotension. Finally, cardiovascular examination including exercise stress test should be performed after 15 years or sooner for those with additional cardiovascular risk factors.

Diabetic care plans may be the cornerstone of effective deterrence of DKA. Patients should be educated and motivated for frequent blood glucose monitoring. This should be done 2 to 3 times at 30-minute intervals before exercise to trend direction of blood glucose levels and thereafter every 30 minutes during exercise. Additional monitoring should be done every 2 hours for up to 4 hours postexertion to monitor for delayed hypoglycemia. For those participating in sports late at night, monitoring should occur at minimum directly before sleep and immediately upon waking, with some recommending one time monitoring during the night.

Predetermined blood glucose levels should be set with the patient’s physician and athletic trainer for barring participation from play. Generally, if the pre-exercise level is less than 100 mg/dL, carbohydrate supplementation should take place. If levels are over 180 mg/dL, the athlete should consume a noncarbohydrate containing fluid to prevent dehydration.

There is a multitude of specific issues regarding insulin use and monitoring in the athlete, and detailed knowledge will help prevent medication misuse and over- or undertreatment before participation. Administration should be subcutaneous and not intramuscular, as the intramuscular route may lead to fast absorption and high insulin peaks during activity. This can be attributed to increased blood flow to the musculature during sport participation as well as the effect of heat on absorption rates. Care must be taken in extreme heat environments, sauna, whirlpool, and hot shower after injection. Cold will have opposing effects on absorption, so ice packs and other cold exposure should similarly be avoided.

Athletes with insulin pumps should change infusion sets 2 to 3 times weekly to avoid skin and infusion site irritation. It also must be recognized that extreme temperatures, generally below freezing or above 86 degrees F, can reduce insulin activity. Therefore, this type of exposure should prompt replacement of the insulin-filled cartridge and infusion set. Other issues to consider with insulin pump therapy include damage during contact sports, disconnection during vigorous movements, and infusion set displacement from excessive sweating by deactivating the pump adhesive.

The diabetic patient must carefully make his or her travel preparations in conjunction with the health care team and athletic trainer. A diabetic patient is allowed to travel on an airplane with carefully labeled diabetic supplies. A travel kit should include unused syringes, blood glucose meters, test strips, lancets, alcohol swabs, insulin, insulin pump if needed and supplies, glucagon emergency kit, and ketone testing supplies. The athlete should generally have at least 2 times as much medication and testing equipment that is thought to be needed. Supplies should be carried with the person at all times and not stowed underneath an airplane. Additionally, extra prescriptions for these supplies should be carried with the athlete as a precaution. Prepackaged meals or snacks should be available, especially if food will not be available for any
period of time. A letter from the athlete’s physician stating the medical condition and necessity of supplies as well as health insurance card and emergency contact numbers should be included in the travel kit. An identification card stating medical condition of diabetes may also be helpful, and, finally, if traveling abroad, it is advisable to learn basic phrases that will alert natives that the patient has diabetes or needs sugar, water, insulin, or health care.8

SUMMARY

DM is a chronic endocrine disorder affecting many children, adolescents, and young adults participating in athletics. If not properly managed, diabetes can lead to many serious complications during exercise, including hypoglycemia, hyperglycemia, and potentially lethal DKA. All individuals directly involved in the care of a diabetic athlete should be aware of the clinical signs and symptoms of hyperglycemia and DKA, and if suspected, patients should be transported to the nearest hospital monitored, with an NS infusion, and treated according to recommended guidelines. It is crucial that all diabetic athletes work with their families, physician, and trainers to create individualized plans of treatment according to the level of activity and severity of disease, as education and prevention are paramount in avoiding most severe complications.

REFERENCES