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Improving Exercise Induced Hypoglycemia in Insulin-Dependent Type 1 Diabetes Mellitus

Madison Orton

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Improving exercise induced hypoglycemia in insulin-dependent type 1 diabetes mellitus

Madison Orton

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What is type 1 diabetes?

Insulin-dependent diabetes mellitus (IDDM), otherwise known as type 1 diabetes, is currently one of the most prevalent autoimmune conditions, affecting over 30 million individuals worldwide (You & Henneberg, 2016). According to the American Diabetes Association, this number is rapidly on the rise with an estimated prediction of 40,000 new diagnoses per year in the United States alone (ADA; 2017).

Under healthy conditions, the endocrine and central nervous systems intricately function together to maintain metabolic and glucose homeostasis throughout the body (Aronoff et al., 2004; Raman, 2017). Following a meal, nutrients from the foods consumed are absorbed in the gastrointestinal (GI) tract, then into the blood stream, which leads to an increase in blood glucose levels, triggering the release of the hormone insulin from pancreatic islet β -cells (Scarlett & Schwartz, 2015). The insulin released functions to signal glucose uptake into liver, muscle, and fat cells where it can be stored or utilized for energy (Wilcox, 2005). In conjunction, the brain-centered glucoregulatory system (BCGS) receives and integrates various nutrition signals, plays a role in inhibiting liver glucose production, and facilitates both insulin-dependent glucose uptake and insulin-independent glucose disposal (Scarlett & Schwartz, 2015). In turn, these complex processes are able to regulate and maintain healthy levels of blood glucose. However, in type 1 diabetes, a combination of genetic predispositions and environmental triggers lead the immune system to produce autoantibodies that misperceive insulin producing β -cells as invaders and destroy them (Atkinson, 2012). With a widespread lack of insulin, the glucoregulatory system is disrupted and glucose is unable to enter cells. Instead, glucose accumulates in the blood stream leading to hyperglycemia, which manifests in a variety of symptoms including excessive hunger, thirst, and urination, unintentional weight loss, blurred vision, fatigue,

weakness, irritability, and mood changes (Mayo Clinic, 2017). If type 1 diabetes is not promptly recognized and treated, prolonged elevated blood glucose levels can lead to diabetic ketoacidosis (DKA), in which a lack of insulin provokes increased secretion of glucose from the kidney and liver, amino acids from muscle, and free fatty acids from adipose tissue, in turn increasing blood acidity, reducing blood flow, and inducing severe dehydration (Raghupathy, 2015). Merely a century ago, a diagnosis of T1D was fatal within weeks or months, even when following a strictly low carbohydrate diet, and individuals would develop DKA and their cells would be essentially starved of energy (Rosenfeld, 2002) Around the 1920s, however, the discovery of exogenous insulin, made possible by contributions from several scientists, Frederick Banting, Charles Best, Jon Macleod, and James Collip, changed the prognosis (Rosenfeld, 2002). With administration of exogenous insulin, the gap in the glucoregulatory system can be artificially restored, making it possible for individuals diagnosed with type 1 diabetes to live relatively long and healthy lives, that is, with diligent 24/7 management.

Management

When it comes to managing type 1 diabetes, every individual follows different protocols and has unique insulin requirements due to the complex nature of the condition. Therefore, working with an endocrinologist and diabetes educator in the management of this condition is important to establish and adjust treatment plans and care as needed.

Day to day, individuals with type 1 diabetes must frequently monitor their blood glucose levels via finger sticks (approximately 10-15 times a day) or by subcutaneous continuous glucose monitoring (CGM) (National Diabetes Education Initiative, 2016). Target blood glucose ranges can vary based upon a variety of factors including, age, comorbid conditions, duration of diabetes, and other considerations; however, the ADA guidelines broadly recommend a blood

glucose range of 80 to 130 mg/dL pre-prandial, <180 post-prandial, and a 3-month average of <154 mg/dL or 7.0%, measured by a glycated hemoglobin (HbA1c) levels (2018).

In addition to monitoring blood glucose levels, individuals must measure and count all carbohydrates consumed and administer intensive bolus-basal insulin therapy via either multiple daily injections (MDI) or a continuous subcutaneous insulin infusion (CSII) pump (ADA, 2015; Mianowska et al., 2011). When using MDI, individuals inject rapid or short-acting bolus doses of insulin prior to meals and to correct high blood glucose levels, based upon insulin to carb and correction factor ratios, in addition to long-acting insulin once per day (Subramanian et al., 2016). When using CSII, individuals wear a small device that continuously administers preprogrammed basal doses of fast-acting insulin and allows for bolus doses with meals and blood glucose corrections via a small cannula under the skin (Subramanian et al., 2016). For many, insulin pump therapy is much more flexible for daily life, as basal insulin doses can be easily adjusted as needed when taking into account the multitude of factors that can affect blood glucose levels and insulin requirements, including physical activity, stress levels, illness, other medications, hormone levels, weather conditions, time of day, etc. (ADA, 2015; Mianowska et al., 2011). With these extensive factors that can influence various aspects of type 1 diabetes management, achieving adequate control can be difficult and exhausting.

Impacts on the body

Although individuals with well-managed type 1 diabetes can live relatively long and healthy lives, various structural and physiological changes occur within these individuals and can be exacerbated by inadequately controlled blood glucose levels. It is thought that due to prolonged exposure to high and low blood glucose levels over time, the body undergoes

extensive amounts of oxidative stress leading to widespread maladaptations and increased risk for comorbid conditions (Arif et al., 2018; Giacco et al., 2010).

A majority of hyperglycemia related changes that have been observed in individuals with type 1 diabetes occur within macro and microvasculature. Although mechanisms of these changes are not completely understood, research suggests that chronic inflammation and altered signaling for intracellular regulation of calcium and vascular endothelial growth factor (VEGF) may play key roles in the increased risk for development of vascular complications associated with type 1 diabetes (e.g. hypertension, stroke, myocardial infarction, coronary and peripheral artery disease) (Stehno-Bittel, 2012). Additionally, within the musculoskeletal system, several changes, including reduced bone mineral density and turnover, impaired skeletal muscle regeneration following injury, as well as altered mitochondrial structure and bioenergetics, have been discovered (Krause et al., 2013; Maggio et al., 2010; Monaco et al., 2018; Parajuli et al., 2015). Because the musculoskeletal system is integral to providing structural support and facilitating movement, these changes can be detrimental, as they put individuals at greater risk for fractures, delayed injury recovery, and reduced physical performance among other negative impacts (Krause et al., 2013; Stehno-Bittel, 2012).

On the other hand, acute and prolonged exposure to hypoglycemia have also been found to have diverse impacts on the body, primarily affecting the cardiovascular and central nervous systems. Principally, when it comes to the acute effects of hypoglycemia on the cardiovascular system, various mechanisms related to counter regulatory hormones and autonomic system activation lead to extensive physiological and pathophysiological changes (Yang et al., 2016). Electrophysiologically, T waves become inverted or decreased in magnitude, QT intervals are prolonged, and ST segments are depressed (Yang et al., 2016). Hemodynamically, peripheral

systolic blood pressure, heart rate, cardiac output, and myocardial contractility increase, while peripheral artery resistance and central blood pressure decrease (Yang et al., 2016). Additionally, prothrombotic and inflammatory effects have been found throughout the vasculature. With these various changes occurring in the cardiovascular system during hypoglycemia, recent research suggests that there may be long-term adverse consequences when it comes to prolonged exposure such as increased risk for cardiovascular events, dysrhythmias, and mortality (Paty, 2015).

In conjunction with acute cardiovascular responses, hypoglycemia impacts the central nervous system due to a lack of glucose in the brain, which is its primary source of fuel (Rooijackers, 2016). With severe decreases in blood glucose levels, brain glucose concentrations can become substantially lower than the average 15-20% leading to neuronal cell death, oxidative stress, and alterations in brain activity measured by electroencephalography (Jensen et al., 2014). These physiological changes can manifest in a variety of symptoms, including impaired cognitive function, confusion, dizziness, shakiness, stupor, etc. (Tanoli et al., 2011). Further, severe or extended acute hypoglycemic episodes can rapidly become life-threatening, provoking loss of consciousness and seizures (Jensen et al., 2014; Tanoli et al., 2011). Without prompt administration of subcutaneous exogenous glucagon, an unconscious, seizing individual with hypoglycemia can go into a coma and die (Jensen et al., 2014). Long-term, research has suggested that prolonged exposure to hypoglycemia can additionally generate hypoglycemia unawareness, recurrent hypoglycemia, memory deficits, and various neurocognitive impairments (Northam et al., 2001; Rooijackers, 2016).

Due to the dynamic widespread effects of both hyper and hypoglycemia on the body, it is imperative for individuals with type 1 diabetes to reduce their exposure to abnormal blood

glucose levels and maintain euglycemia as much as possible. One of the most emphasized means of achieving adequate blood glucose control is regular physical activity and exercise (Riddell et al., 2017).

Exercise

Widespread positive health benefits of exercise have been elucidated extensively in research. For example, regular exercise across the lifespan has been associated with decreased risk of various conditions, such as obesity, cardiovascular disease, osteoporosis and osteoarthritis, some cancers, and can improve mental, heart, muscle, bone, and joint health (Singh, 2002; Warburton et al., 2006). For individuals with type 1 diabetes, routine exercise is additionally highlighted as a means of improving blood glucose control, lowering total daily insulin requirements via greater insulin sensitivity, and reducing risk of various complications previously discussed (Stehno-Bittel, 2012).

Following exercise recommendations can be challenging, however, for individuals with type 1 diabetes due to increased blood glucose variability and more frequent bouts of hypoglycemia that are often induced by various types of activity. In a healthy individual, glucoregulation during moderate to high-intensity exercise is maintained, as glucose uptake at active muscles considerably increases, circulating insulin levels are reduced, and hepatic glucose production is upregulated (Camacho et al., 2005). However, in individuals with type 1 diabetes, glucose production is reduced due to an inadequate hepatic response and plasma insulin levels fail to be decreased while glucose uptake remains elevated (Camacho et al., 2005). Furthermore, accelerated subcutaneous insulin absorption and action have been noted with exercise in individuals with type 1 diabetes (Camacho et al., 2005). Consequently, these impaired

glucoregulatory processes lead to greater hypoglycemia risk during exercise and up to 48 hours following an exercise bout (Basu et al., 2014; Camacho et al., 2005).

When comparing anaerobic versus aerobic exercise, each has slightly different impacts on blood glucose levels in type 1 diabetes. With anaerobic exercise, such as weight lifting, sprinting, and jumping, blood glucose levels often initially increase due to metabolic and hormonal responses (Hargreaves, 2000; Turner et al., 2015). Particularly, surges in plasma noradrenaline and adrenaline during anaerobic exercise have been shown to induce β -adrenoceptor mediated glucose release from the liver, raising blood glucose levels (Howlett et al., 1999). This response, however, is typically only observed with one to two sets of short-duration resistance exercises, while three or more sets induce more utilization of circulating blood glucose to sustain prolonged periods of resistance exercises (Turner et al., 2015; Yardley et al., 2013). In turn, with extended periods of anaerobic exercise, blood glucose levels are more stable and may increase or decrease only slightly, depending on intensity and duration. In contrast, aerobic exercise has been extensively linked to hypoglycemia both during and following activity.

With aerobic exercise, the body relies primarily on free fatty acids, muscle glycogen, and blood glucose as fuel sources; therefore, with continued exercise, blood glucose levels steadily decrease (Hargreaves, 2000). Having initial blood glucose levels around 120mg/dL, within 15 minutes of the onset of aerobic exercise, blood glucose levels begin to drop at a rate of approximately 1-2mg/dL/min which can rapidly increase proportional to intensity and duration (Tansey et al., 2006; Yardley et al., 2013). In order to increase blood glucose levels to the healthy range, 15g of oral glucose supplementation is necessitated every 15 minutes, however, during aerobic exercise this is often inadequate, leading to prolonged hypoglycemia that is

difficult to treat and can quickly become critical (Tansey et al., 2006). Additionally, not only does aerobic exercise induce rapid decreases in blood glucose during activity, it also increases incidence of nocturnal hypoglycemia during sleep (Tamborlane, 2007). Since counterregulatory-hormone responses that occur with hypoglycemia are blunted during sleep, nocturnal low blood glucose levels can pose significant danger, as individuals do not perceive symptoms and may sleep through episodes, especially during deep sleep phases (Jones et al., 1998). For these reasons, it is a common phenomenon for individuals with type 1 diabetes to avoid exercise due to a fear of hypoglycemia as well as undereducation about how to manage blood glucose levels with the added impacts of different activity types, intensities, and durations. Therefore, it is essential to understand how blood glucose levels can be maintained near euglycemia during and post exercise in order to improve overall health, condition management, and quality of life for individuals with type 1 diabetes.

Reducing blood glucose variability

Despite the prevalence of type 1 diabetes and importance of regular exercise in overall health and condition management, research surrounding glycemic control and exercise is somewhat limited. However, several areas of focus in recent literature include insulin therapy modification, pre-exercise carbohydrate supplementation, order of exercise type, and the use of closed-loop pump technology.

An investigative study by West and colleagues (2010) looked at the effects of 25%, 50%, and 75% pre-exercise rapid-acting basal insulin reductions on blood glucose level patterns both during and throughout a 24-hour period following 45 minutes of running at 70% of maximal oxygen uptake (VO_{2max}). Neither 25% nor 50% were adequate reductions in insulin, leading to hypoglycemia. However, a 75% insulin reduction best preserved blood glucose levels during and

following aerobic exercise. In a more in-depth follow up study, West and colleagues (2011) administered low glycemic index carbohydrate supplementation prior to a 30, 60, 90, or 120-minute rest period in addition to a 75% reduction in basal insulin dose prior to, during, and 3 hours following running at 70% VO₂max for 45 minutes. With both carbohydrate supplementation and insulin reduction, adequate blood glucose levels were most favorably preserved in the group that had a 30-minute rest period. Particularly, decreased carbohydrate oxidation and increased lipid oxidization likely contributed to sustained adequate blood glucose levels due to a shift toward greater dependence on fat utilization for energy (West et al., 2011). Although insulin adjustment and carbohydrate supplementation can diminish hypoglycemic episodes during and post-aerobic exercise, reduced basal insulin rates can induce hyperglycemia prior to exercise, which was observed in these studies, and is not favorable due to associated health risks. Additionally, taking the time to reduce insulin, supplement carbohydrates, and factor in a period of rest prior to exercise requires time, planning, and diligence, which is not always feasible in day to day life.

From a different angle, another relatively recent area of interest when it comes to glycemia management is the order in which one performs different types of activity. Considering the divergent metabolic and hormone responses between anaerobic and aerobic exercise, Yardley et al. (2012) set out to determine whether performing aerobic prior to anaerobic exercise, or vice versa, has an impact on glycemic control in individuals with type 1 diabetes. In the study, a group of physically active individuals with adequately controlled type 1 diabetes ($HbA_{1c} = 7.1 \pm 1.0\%$) performed either 45 minutes of 60% VO₂max running prior to 45 minutes of a resistance training circuit program, or in the reverse order. In the aerobic before resistance (AR) condition, an immediate drastic drop in plasma blood glucose levels was observed which slightly recovered

as resistance exercise progressed and into the first hour of recovery. In the resistance before aerobic (RA) condition, however, blood glucose levels were stable during the first exercises and more slowly decreased during aerobic exercise, maintaining euglycemia into the first hour of recovery. Additionally, during the 12 hours following exercise, the AR group experienced a drop in blood glucose around 1:00am and much lower glycemia overnight than the RA group, which was more stable. Although RA blood glucose levels were more stable both during and following the exercise program, it is important to note that the study reports an equal number of hypoglycemic episode between the two groups; however, RA hypoglycemic episodes were significantly shorter in duration than AR (48 ± 68 min; 105 ± 116 min). Due to these result, this study does not permit a conclusion that resistance before aerobic exercise eliminates hypoglycemia, but it does suggest that it may contribute to reducing the time spent in a hypoglycemic state.

Although the aforementioned research focused on mediating exercise induced hypoglycemia generate helpful advice for individuals with type 1 diabetes, nothing can replace the intricate control system of healthy pancreatic β -cells when it comes to glucoregulation. Next best, however, is a hybrid closed-loop pump system, or artificial pancreas, which is currently one of the leading focuses of research when it comes to type 1 diabetes management. Closed-loop pump systems integrate CGM sensor readings into algorithms developed to functionally adapt basal insulin delivery in response to blood glucose trends and predictions analogous to that of a working pancreas in order to adequately maintain euglycemia. At present, many studies have demonstrated the efficacy of such systems under simple, controlled conditions, yet they must be capable of adapting to more complex scenarios and the diverse factors that influence blood glucose levels and insulin requirement of individuals with type 1 diabetes, especially exercise.

For this reason, several recent studies have investigated the function of closed-loop pump systems under various exercise conditions. There are two types of closed-loop systems being tested currently, single-hormone automated insulin delivery and dual-hormone automated glucagon and insulin delivery systems. In a recent study, Castle and colleagues (2018) compared the two closed-loop pump systems, predictive low insulin suspension, and traditional open-loop pump therapy and their impacts on glycemia during and several hours following in-clinic moderate-intensity aerobic exercise. In relation to blood glucose levels with traditional pump therapy, predictive low glucose suspension and both closed-loop systems reduced hypoglycemia, with the dual-hormone closed-loop pump system producing slightly superior glycemic control. However, the addition of glucagon to treatment largely increases the cost and complexity of the system and has been observed to induce mild adverse symptoms, such as nausea (Castle et al., 2018). While the results of this study are promising for the use of closed-loop systems in reducing exercise-induced hypoglycemia, the exercise took place in a clinic, which may reduce the applicability of results. With a more realistic approach, Breton and colleagues (2017), compared the use of an automated insulin delivery closed-loop system to a typical open-loop physician monitored system during a five-day ski and snowboard camp for adolescents with type 1 diabetes. Despite prolonged activity in a cold, high altitude environment, participants using the closed-loop system experienced significantly shorter and less frequent episodes of hypoglycemia, required fewer carbohydrate supplement treatments, and achieved overall tighter glycemic control during and post exercise, as well as throughout the night. Altogether, findings from these recent studies are revolutionary in the field of type 1 diabetes management; however, there are several limitations to take note of, particularly related accessibility.

Limitations and next steps

When individuals are diagnosed with type 1 diabetes, initial consultation and education occurs with an endocrinologist; however, this transmission of essential information often occurs in a very expedited manner during a highly stressful time which can be overwhelming for individuals, or care takers of individuals with type one diabetes (Silverstein et al., 2005). Further, due to the complexity of the condition, additional continued care and extensive education is vital to achieving adequate management. In many cases, though, individuals do not have access to a team certified professionals, including a dietician, nurse, physician, and mental health care provider, to assist them in developing and adapting treatment plans (Peyrot & Rubin, 2008). Without this support, many individuals are undereducated about their condition and how to successfully manage it.

Additionally, for many individuals with type 1 diabetes, having access to advanced technology, such as CGMs and insulin pumps is limited, and simply obtaining the basic necessary supplies for management, including insulin, blood glucose monitors, test strips, and needles can be burdensome due to cost. According to a press release from the Centers for Disease Control and Prevention (2011), on average annual medical costs for a child with type 1 diabetes were greater than \$9,000 per year. Since 2011, however, costs for managing type 1 diabetes have skyrocketed, with insulin being the sixth most expensive liquid in the world (Hua et al., 2013; Melvin, 2016). With many individuals who have type 1 diabetes struggling to afford insulin, a hormone essential to their survival, in addition to their other fundamental medical supplies, access to new technologies is severely limited. In order for the promising findings of recent research in reducing exercise-induced hypoglycemia to help individuals with type 1 diabetes achieve adequate glycemic control and improve quality of life, widespread problems

regarding accessibility to education and care must first be addressed, which requires greater advocacy and awareness about the condition.

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