Euglycemic Diabetic Ketoacidosis: A Case Study Review for Educating Type II Diabetics

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Introduction

Diabetic Ketoacidosis (DKA) is typically discussed in the scope of Type I diabetics and insufficient insulin control. However, with the advent of new medications and their pharmacodynamics, we must start to rethink how we educate our patients. In this case study review, we will look at how this patient was initially diagnosed, treated, and educated. In addition, we will discuss ways of preventing the onset of Euglycemic diabetic ketoacidosis in Type II patients in the future.

Case Study

The patient is a 63-year-old white male, diagnosed with adult-onset diabetes at the age of fifty-eight. Prior to the diagnosis of diabetes there was no previous medical history except for Idiopathic Thrombocytopenia Purpura (ITP) in childhood. The patient had a 30-pack year smoking history, quitting in 2014. Patient drinks alcohol, consisting of light beer. Drinks 6-8 16-ounce beers on weeknights and 12+ per day on the weekends. At the initial diagnosis, the patient weighed 220lbs. Relevant family history of Type I diabetes, father early adult onset, Type II diabetes, mother, adult late onset. Paternal and Maternal sets of grandparents had diabetes, type unknown.

Initial Diagnosis

This patient was initially diagnosed based solely on a HgbA1c reading greater than 7.0. The patient was started on Trulicity 0.75mg, diet changes and exercise. After 3 months, the patient had lost over 20 lbs. and began walking five miles a day, averaging 5 days a week. However, despite being on Trulicity, dietary changes and incorporation of exercise, the patient's A1c rose to over 11.5.

When making an initial diagnosis of diabetes in adults, it is important to determine whether it is Type I versus Type II. In order to successfully do that we first have to remove the myth that Type I is only diagnosed in children and adolescents. Type I diabetes has been diagnosed in 1.3 million people in the U.S. with more than 50% being diagnosed in adults [1,2]. Type I diabetes diagnosed in adulthood is also referred to as Latent autoimmune diabetes in adults (LADA) [3].

The difficulty with diagnosing the type of diabetes in adults is that most adults do not present with the common signs and symptoms associated with Type I diabetes because it is thought that they have a different phenotype of Type I compared to the phenotype seen in children and adolescents. Research continues to demonstrate that type 2 diabetes is the predominant diabetes in adults, especially later in life; however genetically defined type I diabetes is noted to be consistently diagnosed within the first 6 decades of life [2]. To be diagnosed as LADA, the patient needs to meet the following criteria: 1) onset of diabetes after age 35, 2) positive test for at least one auto antibody, and 3) insulin started within 6 months of diagnosis [3].

Rather than only looking at the A1c and presenting symptoms, additional lab studies should be ordered and reviewed before identifying the type of diabetes an adult has. The two most used biomarkers to determine presence of Type I diabetes are the C-peptide and Islet autoantibodies [2]. The C-peptide is stored in the pancreas, specifically in secretory vesicles in the islets of Langerhans and is an amino acid that connects the alpha and beta chains of proinsulin. In the Golgi apparatus, c-peptide is removed from the alpha and beta chains, creating the mature insulin molecule. When glucose stimulates the beta cells of the pancreas, C-peptide and insulin are equally released. Normal circulating levels of C-peptide in a fasting state are 0.8 to 1.8 ng/ml. Low C-peptide levels are correlated with beta cell failure and Insulin deficiency indicating a diagnosis for Type I diabetes [4]. Auto-islet antibodies help to distinguish between the classifications of diabetes as well as the three subtypes of Type I diabetes and serve as important humoral biomarkers. There are four primary autoantibodies assessed, Autoantibodies to insulin (IAA), glutamic acid decarboxylase (GADA), tyrosine phosphatase-like protein IA-2 (IA-2A), and zinc transporter 8 (ZnT8A) to determine the presence of Type I diabetes. Assessing these specific biomarkers has shown 93-96% specificity for acute onset Type I diabetes and slow progressive Type I also known as latent adult-onset Type I. It needs to be noted that for patients already taking insulin, interpreting the IAA results can be challenging as the test does not recognize the difference between innate insulin and exogenous insulin [3].

Treatment

As previously mentioned, this patient was started on 0.75mg Trulicity weekly, diet changes and exercise regimen. The patient began eating a healthier diet in that he cut out simple sugars and sodas; however, he continued to eat potatoes and breads but at a reduced amount. He began walking 3-5 miles a day weather permitting and incorporated muscle toning/strength exercises two times a week.

Diet and Exercise

No matter the type of diabetes being addressed diet and exercise diet are important pillars that must be discussed, and their importance emphasized. Dietary changes must be tailored to the patient's preferences and incorporate a cultural focus. The focus of dietary changes should be geared towards healthy eating, lowering cholesterol and blood pressure if necessary and maintaining a healthy body weight [5]. There are many dietary plans that are marketed towards people with diabetes. The key to compliance will be to find or create a plan that meets the patient's needs while staying within their personal, religious, cultural, or regional preferences.

In a recent article by Zahalka, et al. [6], 34.3% of American's diagnosed with diabetes are physically inactive and only 23.8% meet the 150-minute portion of the physical activity guidelines established by the American Diabetes Association. As providers, we are fully aware of the benefits of exercise, therefore we must ask the question what is keeping patients from exercising? Do our patients understand what the term exercise means? Many patients feel the walking they do on the job or in their daily routine counts as exercise. We must educate them that aerobic exercise such as walking only counts when the heart rate raises and is sustained for greater than 20 minutes. We also need to address any physiological, psychological, and socioeconomic barriers to exercising [6].

Physiological barriers are barriers created by the patient's own body where modifications need to be made. Physiological barriers can include issues with weight, poor overall fitness at the onset, respiratory, anemia, painful joints, balance concerns, neuropathy, and visual concerns. All these concerns can be addressed and met with modifications. Physical fitness plans that are tailored to the individual needs and preferences will make them more successful. Encouraging them to start with small goals building up to the 150 minutes per week [6]. Psychological barriers typically center around poor self-esteem and depression. Positive encouragement and advising them to work out with likeminded individuals will help to slowly increase their confidence raising their self-esteem. It is also important to note that exercise has been shown to successfully assist with the maintenance and control of depression.

Combating the socioeconomic barrier may be one of the hardest to overcome. Socioeconomic barriers can include no safe place to exercise outside of their home, no transportation to facilities or parks to no financial means to buy clothes, shoes, or equipment. The first way to combat this barrier is to assure the patient that they can use simple items within their household to get started. My favorite regiment I discuss with patients is what I have termed the commercial workout. I tell them to have two 16oz cans of canned goods by their chair. When a commercial comes on, they start with bicep curls, when the next commercial comes on they change to triceps curls and with additional commercial another type of upper body workout. They can walk in place for the duration of a commercial or do squats, lunges for the lower body work out. As their ability increases, then they perform one exercise through 2 commercials and so forth. Other suggestions can include free exercise apps if they have smartphones that are low intensity. The key is getting the patient excited about being able to do something rather than nothing and as they make progress and see the subtle changes, they tend to increase their ability to perform exercises.

Medications

Medication management is the third pillar of diabetes treatment. Depending on the type of diabetes diagnosis and any co-morbidities will help guide the provider to which medication to start treatment with. For type I diabetes, the only preferred medication is Insulin. For Type II diabetes the provider can choose between an oral or an injectable depending on the patient preference and any other mitigating factors. Some of the oral medications can be used for monotherapy while others must be used as an adjunct. All the injectables can be used as monotherapy. Metformin (Glucophage) which is a Biguanide has historically been the first line treatment for Type II diabetes. It inhibits the liver from producing any glucose and stimulates the tissue uptake receptors to intake glucose into the tissues [7].

Based on the alcohol intake with our patient, Metformin could not be used as the first line medication management. Patients who are alcoholics are at an elevated risk of developing lactic acidosis when taking metformin and other anti-diabetic medications such as sulfonylureas [8]. Therefore, he was started on Trulicity at 0.75mg weekly. The dosage management plan for Trulicity is to start at 0.75mg Subcutaneously (SC) weekly with an increase by 1.5mg every 4 weeks to a max dosage 4.5mg weekly. This patient was not followed up by a provider until 6 months later when he was assigned to a new provider. At that time, he had not shown much improvement to his A1c despite continuing with weight loss, dietary control, and exercise. The Trulicity was increased to 1.5mg once a week with a follow up in 3 months. At the end of 3 months only a slight decrease was noted in the patient's A1c. He was increased to 3mg SC weekly and started on Lantus 28 units SC nightly. The decision to add insulin versus another anti-diabetic medication was based on his family history of the father having early adult onset. It was presumed that there was more of genetic component versus lifestyle component to the patient's diabetes. However, no additional blood work was performed such as the C-peptide and antibodies to confirm this assumption. The patient stayed on this treatment plan for a period of 2 years with the A1c staying between 7 and 8.

Trulicity is a GLP-1 agonist, which enhances the incretin hormones Glucagon-like peptide 1(GLP-1) and Glucose-Independent Insulinotropic Polypeptide (GIP) inactivation after an ingestion of glucose by the incretin system. This forces the pancreas to release more insulin. In addition, it reduces gastric emptying, thereby preventing glucagon production from the pancreatic alpha cells and decreases pancreatic beta cell cellular death [9]. GLP-1 agonists are considered the first line treatment for patients diagnosed with diabetes if they cannot tolerate or have a contraindication to the use of metformin [10]. Insulin use in Type II Diabetes is started when patients have not obtained appropriate glycemic control using anti-diabetic agents. The purpose is to reduce the long-term effects on multiple body systems of having elevated glucose levels that can lead to glucose toxicity and increased morbidity and mortality rates [11]. A study conducted in 1985 as cited in White, et al. [11], the use of insulin in the treatment of Type II diabetes, moderately reversed the post binding defect in peripheral insulin action, producing basal hepatic glucose output that returned to near normal levels, and boosted insulin secretion, thereby allowing the maintenance of normal glucose controls. The mean daily insulin usage decreased by 23% after 2 weeks of therapy.

There is no set guideline to which type of insulin to start a Type II diabetic patient on. The goal of insulin therapy is to mimic the body's own phases of insulin secretion. Prandial insulin is injected prior to eating a meal and offers the patient more flexibility with their treatment plans. Basal insulin is a once-a-day or twice a day injection and may be used in conjunction with prandial or by itself. Several studies have concluded that glargine rather than NPH taken nightly has a reduced risk of hypoglycemic incidences [11]. The patient was initially started on twenty-eight units nightly of Lantus, which is glargine. The initial dosing schedule for glargine per Epocrates [12] is 0.2 units per kilogram per dose. In the article by White, et al. [11], the American Diabetes Association (ADA) recommends providers start at 10 units per dose then titrate upwards till desired glucose control. Starting lower, reduces the incidences of nighttime hypoglycemic reactions.

After a period of stabilization, our patient's A1c started to rise closer to nine partly due to decrease in exercise and changes in dietary habits. Initially there were no changes in the patient's treatment regimen except to encourage to return to a level of activity and dietary modifications. After losing more weight and falling back into the mid 190's, the patient began to experience hypoglycemic events during the night where his glucose would drop into the forty's. The patient was asymptomatic except for feeling clammy upon awakening. Patient would eat some form of simple sugar to raise sugars and then would begin his day. It is important to note that the patient did not routinely check his blood sugars using a glucometer. Once the patient began experiencing afternoon fatigue, it was advised for the patient to check his sugars three times a day. It was then learned that his fasting am sugars would be between 40 and 59 and his mid-afternoon readings would be as high as 355. At this time, it was suggested to the patient by his provider to go to a twice a day Lantus injection splitting the current dose of twenty-eight units to 14 in the am and 14 in the pm. The patient was opposed to increasing the number of injections and was therefore started on Farxiga also known as dapagliflozin which is a Sodium glucose transport 2 (SGLT2) Inhibitor.

SGLT2 Inhibitors act in the proximal tubules of the kidneys by blocking the SGLT2 proteins from allowing the reuptake of glucose from the proximal tubule lumens thereby decreasing the renal threshold and promoting excretion of glucose in the urine. Treatment with the SGLT2 inhibitors creates a ketogenic environment where the body goes into mild ketogenesis. The interference with glucose reuptake and proximal sodium reabsorption causes natriuresis which also lowers blood pressure and can induce additional weight loss. SGLT2 inhibitors have a 3-fold risk for developing ketoacidosis. The patient may present with signs of diabetic ketoacidosis (DKA) which include malaise, generalized weakness, nausea and vomiting, mild confusion or disorientation and glucose levels greater than 300 mg/dl. Euglycemic diabetic ketoacidosis (eDKA) presents as diabetic ketoacidosis except that glucose levels are less than 250 mg/dL. Prior to starting a patient on a SGLT2 Inhibitor, an assessment for the risk of developing ketoacidosis should be conducted [13].

The patient started taking Farxiga 10mg daily. He also began wearing a continuous glucose monitor that helped him to keep a closer track of the trends his glucose was taking. After being on the medication for 2 weeks, his glucose levels had stabilized to the point he stopped taking his Lantus at night. At the end of the first month, despite his glucose levels being within normal ranges, he began to experience extreme tiredness, decreased energy levels and decreased appetite. He also developed shortness of breath when speaking or walking only a few steps along with chest discomfort. His symptoms began to interfere with his exercise routine and ability to work from home. The patient was taken to the Emergency room after a telehealth visit, where the primary care provider was concerned the patient may be experiencing a myocardial infarction.

Upon arrival to the emergency room, he was quickly triaged and an EKG, labs, and an arterial blood gas (ABG) were obtained. His anion gap was 28 and his pH level was 7.1. The patient was diagnosed with eDKA and admitted to the Critical Care Unit for treatment.

Euglycemic Diabetic Ketoacidosis

Pathophysiology of eDKA

Euglycemic diabetic ketoacidosis (eDKA) is an uncommon occurrence in diabetic patients that was once only relegated to surgical patients, diabetics who became pregnant and those that chose to fast; however increasing incidences are occurring with the advent of the SGLT2 inhibitors. It typically centers around an imbalance ratio between the glucagon and insulin ratio. Risk factors for developing eDKA are fasting, being on a ketogenic diet, alcohol use disorder or any disorder leading to a state of carbohydrate starvation. Patients that have a low body mass index are also at risk for developing it [14]. A study cited in Plewa, et al. [14], showed that only 2.6 to 3.2 % of hospital admissions for DKA were eDKA and those associated with a SGLT2 Inhibitor range from 0.16 to 0.76%. Euglycemic diabetic ketoacidosis consists of the triad of elevated anion gap acidosis, the presence of ketosis, and serum glucose < 250 mg/dL. The development of ketone bodies in eDKA follows the same pathophysiology as in DKA [14]. With DKA there becomes an insulin deficiency causing an increase in the counterregulatory hormones. These 2 factors will trigger the release of free fatty acids from adipose tissue referred to as lipolysis into circulation. The free fatty acids will then undergo a process of hepatic fatty acid oxidation in the liver creating the ketone bodies (beta-hydroxybutyrate and acetoacetate). This oxidation of the free fatty acids results in ketonemia and metabolic acidosis [15]. When a patient goes into metabolic acidosis, that activates respiratory compensation resulting in the sensation of dyspnea, nausea, anorexia, or vomiting. The patient will experience decreased oral intake related to vomiting or nausea, and osmotic diuresis from glucosuria ketogenesis resulting in volume depletion. This will exacerbate elevations in glucagon, cortisol, and epinephrine, worsening lipolysis and increase the formation of ketone bodies [14].

The role of SGLT-2 inhibitors

It is theorized that because SGLT-2 inhibitors cause noninsulin-dependent glucose clearance, hyperglucagonemia, and volume depletion, they more readily cause eDKA [13]. Hyperglucagonemia is where there is an excess level of glucagon secretion. In normal pathophysiology, insulin suppresses glucagon secretion. When this function is inhibited by a lack of insulin control, hyperglucagonemia can occur. Hypoglycemic states are stimulators for the release of glucagon whereas hyperglycemia suppresses glucagon release. Elevated levels of glucagon encourage glycogenolysis, gluconeogenesis, lipolysis and ketogenesis to occur. In DKA, glucagon inhibits malony coenzyme A (CoA) from normally suppressing ketogenesis creating a now ketogenic state. Hyperglucagonemia not in the presence of a SGLT-2 Inhibitor in a Type II diabetic does not typically cause DKA because the levels of insulin although low are sufficient to curb the hepatic producing function [16].

In a study by Dutta, et al. [17] they surmised that in the presence of a SGLT-2 Inhibitor there appears to be a dose relation to the increasing incidence of eDKA due to the increasing excessive release of glucagon. Based on the results of Dutta, et al. [17] and other studies cited in their article, the hypothesis for the increasing incidences of eDKA with the use of SGLT2 is related to it causing the binding of glucagon to the α-cells of the pancreas which increases gluconeogenesis. In addition, it is causing an increase in glucose excretion in the renal system decreasing the overall blood glucose levels in the vascular system. This decrease coupled with a decrease in circulating insulin increases ketone body formation. They continue to state that the true connection between SGLT2 Inhibitors and eDKA remains unclear and additional research as well as education to providers before prescribing SGLT2 Inhibitors is warranted.

Discussion

When reflecting on our case study, three points stand out. The first being how the patient was diagnosed, the second being the long-term use of alcohol and the third being the abrupt stopping of his Lantus. As previously noted in the article, more careful decision making should occur when diagnosing someone as a diabetic. Many of the newer medications on the market are targeted for Type II diabetes and should not be used in Type I diabetics. If a provider diagnoses a patient merely on A1c levels and no other diagnostic criteria including family history, C-peptide, and antibody levels, they could be doing the patient a huge disservice and possibly endeavoring them to harm in terms of adverse reactions. As Nurse practitioners, the basis for our profession is holistic care; therefore, we take pride in looking at the patient from the bigger picture. Nurse practitioners are more apt to think about the patient's family history and utilize the most current evidence base standards for diagnosing. Understanding the increasing incidences of latent adult-onset Type I diabetes, we need to be more careful and do our due diligence so that we appropriately diagnosis our patients ensuring they are being prescribed the correct formulations of medications.

The next area not receiving as much attention as should be is the component of the social history addressing alcohol use. How alcohol affects the body and interacts with medications is something that needs to be taken into consideration with every new prescription and periodically with current medication review. In 2004, The US Preventive Task Force (USPTF) recommended that every patient be screened for alcohol use and not just alcohol abuse because even misuse can place the individual at an increase for morbidity and mortality risk. When surveyed 96% of primary care providers stated they screen for alcohol misuse but only 38% use any approved screening tools. The USPSTF recommends use of one of three screening tools that measure alcohol consumption. These screening tools include the Alcohol Use Disorders Identification Test, Alcohol Use Disorders Identification Test-Consumption, and National Institute on Alcohol Abuse and Alcoholism Single Question which are all available on the USPTF website [18,19].

Historically providers utilized the CAGE assessment which assess for alcoholism; however, the screening tools suggested by the USPTF are more in depth that will help providers identify those patients that do consider alcohol consumption to be a problem; but can be a problem with interactions with their medications. According to Anderson [8], alcohol consumption affects glucose levels and based on how much the patient consumes can either cause hyperglycemia or hypoglycemia. When alcohol is combined with diabetic medications, that increases the patient's the risk for developing hypoglycemia as well as causing the liver to increase production of glucose in the form of gluconeogenesis. Anderson [8] recommends that if patients are going to consume alcohol, they should limit the alcohol consumption to one drink daily for women and two drinks daily for men. One drink is typically defined as a 12 oz beer, 5 oz glass of wine, or 1.5 oz of distilled spirits. All patients regardless of taking medications or not should be advised to never drink on an empty stomach.

The last issue of concern is a concern that bothers many providers and that is when patients stop taking medication on their own without discussing the possible effects of such sudden stoppage with a provider. As we learned throughout this article, insulin has a protective factor against the production of neo glycogenesis from the liver. When the patient abruptly stopped the Lantus, he lost that protective factor which allowed the liver to begin to make glucose to make up for the loss of glucose from the Farxiga. This increased his risk for the development of eDKA. Patients should be strongly advised that before stopping any medication they should discuss the cause and effects with their provider. Although stopping Lantus abruptly does not typically cause severe untoward effects, as seen in our case study there were consequences that could have been avoided if the provider had helped the patient to make an informed decision to slowly decrease the amount rather to stop abruptly.

Summary

With the advent of so many medications hitting the market as providers it is ever more important that we slow down, step back and regain that holistic approach to the patient. When we encompass the patients' medical, family, and social histories we have a better picture of them and can make a more informed decision about a treatment plan that is geared specifically to them. We need to be aware of the nuances that these medications can cause and be cognizant of atypical reactions that the patients may experience. In the case of our patient, he had a positive recovery from the eDKA and has since been started on a new regiment of insulin and antidiabetic medications.

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