

A Case of Hypoglycemia Associated With the Ketogenic Diet and Alcohol Use

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The ketogenic diet, which has become an increasingly popular diet, severely restricts carbohydrate intake to shunt metabolism towards fatty acid oxidation and production of ketones as a fuel source. There have been many studies illustrating the positive effects of a ketogenic diet in weight loss and other benefits; however, the long-term effects and potential adverse events of a ketogenic diet have not been well studied or documented in literature. There are a few case reports of ketogenic diet resulting in hypoglycemia. We report a case of hypoglycemia with a blood glucose of 39 mg/dL and ketosis in a 69-year-old woman who strictly followed a ketogenic diet for nearly one year. She presented with malaise, sugar cravings, and mental foggy, and after intake of alcoholic beverages, was admitted to the hospital with hypoglycemia. She had elevated beta-hydroxybutyrate, and low insulin and C-peptide, all consistent with a starvation ketosis. This case illustrates that adherence to a ketogenic diet for a prolonged period of time, in combination with alcohol intake, can disrupt normal glucose homeostatic mechanisms and result in a significant degree of hypoglycemia. This pattern of hypoglycemia may not present with classic symptoms, most likely partly due to effects of the ketogenic diet on brain function. This case provides insight that supports the need to counsel patients about alcohol intake while on the ketogenic diet. More information is needed on long-term complications of the ketogenic diet on glucose homeostasis in the body as well as in the brain.

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The ketogenic diet is a diet that has become increasingly popular over the past few decades. Initially studied for the treatment for epilepsy in the early 1900s, it has recently gained popularity for weight loss [1]. There are different variations of low-carbohydrate diets that range in carbohydrate intake, and that were popularized by South Beach and Atkins diet. A ketogenic diet is specifically a low-carbohydrate, high-fat diet that aims for a goal of 20 to 50 g of carbohydrate per day, and if possible, no more than 20 g of carbohydrates [2]. This results in a low insulin:glucagon ratio, which causes depletion of glucose and glycogen stores, and reliance on ketone bodies from fatty acids as alternative source of fuel, resulting in ketogenesis, referred to in the diet as achieving a state of *ketosis*. This occurs through the hepatic oxidation of fatty acids. An excess of ketones can result in ketonemia and in some instances, ketoacidosis.

There have been different studies that have shown that the ketogenic diet is overall safe in the short term; however, it is not without risk or adverse side effects [2]. There have been a few case reports and case series of individuals developing hypoglycemia due to the

Abbreviations: BG, blood glucose; PCP, primary care provider.

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ketogenic diet, with most of those reported in children [3-5]. We present a case of a woman who developed starvation ketosis with hypoglycemia while on a ketogenic diet after the consumption of alcohol. We discuss the adverse effects of the ketogenic diet including hypoglycemia and risks of starvation ketosis.

1. Case

A 69-year-old female patient with a past medical history of psoriatic arthritis, Sjogren disease, leukocytoclastic vasculitis, asthma, and anxiety disorder, presented to her primary care provider (PCP) in November 2019 for an annual physical examination. A year prior to this visit, she complained of nausea and abdominal pain, was diagnosed with small intestinal bacterial overgrowth and was encouraged to start a ketogenic diet. Her weight at the start of the diet in December 2018 was approximately 73 kg (160 pounds). She lost about 14 kg over the course of the year. She was consistent with this diet until about 2 weeks prior to her PCP visit in November 2019 when she developed fatigue, mental fogging, and sugar cravings. The cravings led to a few occasions of carbohydrate consumption above her usual “keto” baseline. She subsequently had some alcoholic beverages (reporting a “couple of martinis”) in the 2 days prior to her PCP visit. During the PCP visit, her fasting blood glucose (BG) was checked as part of the routine laboratory panel and it was low at 39 mg/dL. The patient was called by the lab and asked to report back to the PCP office. By that time, she had had breakfast. Her repeat BG measurement was 64 mg/dL. She was given juice, with improvement in her BG level, but no change in her mental fogging or fatigue. The patient was admitted to the hospital for hypoglycemia workup and management.

Admission labs were relevant for a normal basic metabolic panel without metabolic acidosis. Liver function tests were normal, serum albumin was 4.3 g/dL. Her thyrotropin (thyroid-stimulating hormone; TSH) level was 2.48 mU/L. Serum cortisol was 21.8 mcg/dL. Random (nonhypoglycemic state) laboratory tests showed an elevated serum betahydroxybutyrate level of 5.5 mg/dL (reference: 0.0-3.0 mg/dL). Urine analysis showed positive ketones. Other laboratory tests, which included insulin, C-peptide, and proinsulin, were found to be in the reference range; however, these were checked in the setting of a normal admission serum glucose, as listed in Table 1. On the first day of admission, she had a regular meal consisting of pasta, fruit, and part of a sandwich. Afterwards she reported feeling shaky/tremulous and nauseated; when her BG was then checked, it was found to be 59 mg/dL. Her symptoms resolved when she was given dextrose and her BG increased to 105 mg/dL. The patient was then evaluated by the Endocrine team, and a 72-hour fast was started.

The fast started at 8 PM on 11/19/2019 and ended at 10:06 AM on 11/22/2019, thus lasting a total of 62 hours. The fast was stopped per protocol when the patient’s BG dropped to < 55 mg/dL on point-of-care testing. Confirmatory serum BG measurement was 54 mg/dL. The patient did not report symptoms of hypoglycemia then. She ate a meal after the fast was finished. Laboratory specimens were drawn at the end of the fast and values are reported in Table 1. The patient was discharged home with advice to increase her carbohydrate intake to 50 to 150 g/day.

Table 1. Laboratory Workup During Hospital Stay

Serum lab (unit; reference range)	Admission day	End of 72-hour fast
Glucose (mg/dL; variable)	135	54
Insulin (mU/L; 3-25)	12.9	2.8
Pro-insulin (pmol/L; ≤ 8.0)	3.1	<1.6
C-peptide (ng/mL; 0.9-6.9)	2.2	0.6
Betahydroxybutyrate (mg/dL; 0.0-3.0)	5.5	45.1
Insulin antibodies	<0.4	
Sulfonylurea screen	Negative	

2. Discussion

We present a case of a 69-year-old female who presented with hypoglycemia (as defined by a serum glucose of less than 55 mg/dL) [6], after being on the ketogenic diet for 1 year, and ingesting alcohol. Her presentation was atypical in the sense that her symptoms were chronic and nonspecific (fatigue, mental slowing) when her serum glucose was 39 mg/dL, and were more acute (adrenergic) when her serum glucose was 59 mg/dL, with resolution of symptoms after carbohydrate ingestion in the latter setting, but not the former.

The most significant feature of the ketogenic diet is the metabolic achievement of ketosis. A standard ketogenic diet is very high in fat, with 65% to 75% of calories derived from fat, and low in carbohydrates, with 5% to 10% of calories from carbohydrates. Most variations of the ketogenic diet are in the range of 20 to 50 g carbohydrate intake per day, but to ensure ketosis, a maximum intake of 20 g is needed [2, 7]. The physiologic basis behind a ketogenic diet is that by severely restricting carbohydrate intake, BG and insulin levels drop, and the body responds by resorting to the synthesis of ketone bodies. Through hepatic oxidation of fatty acids, acetyl CoA is converted into acetoacetate, β -hydroxybutyric acid, and acetone [7, 8]. β -Hydroxybutyrate and acetoacetate can be metabolized for energy by peripheral tissue, but acetone is not. The ketogenic diet originated in the early 1900s as a treatment for epilepsy, since acetone was found to have an anticonvulsant property [1, 9]. More recently, studies have looked at the properties of a ketogenic diet as an option for weight loss. By entering a state of ketosis, the body breaks down fat as fuel, potentially leading to significant weight loss. The Obesity Medicine Association has endorsed a low-carbohydrate diet as one option for weight loss [10].

The benefits of a ketogenic diet have been widely studied. In one study comparing low-carbohydrate versus low-fat diets, there was no significant difference in weight loss between the 2 groups, but each were efficacious in achieving weight loss [11]. In a study that had obese adults undergo a 12-week ketogenic diet, the average weight loss was 14 kg [12]. Studies reported in the literature over the past few decades have also looked at other potential therapeutic benefits of a ketogenic diet, including in the management of diabetes, polycystic ovary syndrome, neurologic diseases, cancer, inflammation, and cardiovascular risk [1, 13-15].

However, a ketogenic diet is not without risk. Ketogenic diets have been associated with nausea, vomiting, dehydration, and hypoglycemia in the short term, while longer-term effects include disrupted lipid metabolism, hepatic steatosis, hypoproteinemia, mineral deficiency, and nephrolithiasis [16-18]. Also, there are few data on the long-term risks of maintaining a ketogenic diet indefinitely [19]. Part of this may be due to how challenging it is to effectively maintain less than 20 g of carbohydrates in daily intake. There is a fine balance between achieving a state of ketosis and developing ketoacidosis. Severely reduced caloric intake, illness, lactation, and dehydration during a ketogenic diet have been associated with developing ketoacidosis [18, 20, 21]. Despite the popularity of the ketogenic diet, there are few case reports that have highlighted the potential risk of ketoacidosis, indicating it is either a rare complication or underrecognized [22]. One case report documented a nondiabetic ketosis associated with Atkins diet and another associated with ketogenic diet during lactation [21, 23, 24].

There are multiple counterregulatory physiologic mechanisms that protect us from hypoglycemia during fasting or starvation states, making hypoglycemia a rare occurrence in normal individuals [25, 26]. There are few reports of cases of hypoglycemia following a ketogenic diet. In 1964, a case series involving 8 children with “ketotic hypoglycemia” was published, where the clinical presentation was reproduced by “feeding of a low calorie ketogenic diet”. The pathophysiologic basis was thought to be related to failure of adaptation to “fat burning” [3]. In one report of children treated for epilepsy with the ketogenic diet, about 28% were found to develop hypoglycemia (defined in this age population as serum glucose < 40 mg/dL), with younger age being a risk factor [5]. Hypoglycemia unmasking an insulinoma was reported in a case of a 47-year-old after going on a ketogenic diet [4]. In

adults, the feasibility of use of the ketogenic diet in treatment of refractory status epilepticus was reported in one retrospective analysis of 11 patients. Refractory status epilepticus resolved in 73% of subjects. Three of the 11 patients developed hypoglycemia (as defined by serum glucose < 60 mg/dL). Other adverse effects included metabolic acidosis [27].

A particular detail in the patient presented in the current case report is the lack of typical hypoglycemic symptoms upon presentation. This raises the question of whether the ketogenic diet affected her brain response to hypoglycemia. Important work published by Cryer and colleagues in the past 50 years have described the counterregulatory responses to hypoglycemia, and defined the hypoglycemia-associated autonomic failure (HAAF) syndrome as hypoglycemia unawareness, when individuals do not perceive neurogenic warning symptoms of hypoglycemia. There have been debates, with arguments favoring either choice, on whether this response is adaptive (this may protect against brain damage and cardiac arrhythmias) or maladaptive (due to inability to recognize and prevent neuroglycopenic risks to the individual such as falls, seizures, or loss of consciousness) [28]. With respect to specific effects of the ketogenic diet on counterregulatory responses, a recent study in mice showed that there was blunting of glucagon release to hypoglycemia in mice fed a ketogenic diet, suggesting a mechanism for increased risk of hypoglycemia on this diet [29]. On the other hand, the ketogenic diet has been found to protect against hypoglycemia-induced neuronal damage in animals and humans [30, 31]. This may be due to induction of molecular adaptive mechanisms, in addition to attenuation of adrenergic responses to hypoglycemia, while preserving cognitive function. Some of those molecular mechanisms include stabilization of cellular metabolism through increasing cerebral ATP and reducing neuronal excitability [30, 31]. Putting this all together, while the ketogenic diet may increase the risk of hypoglycemia, there seems to be some inconclusive data suggesting that this dietary pattern may blunt some of the counterregulatory responses to hypoglycemia, and may also protect against the deleterious effects of hypoglycemia on the brain, especially acutely. However, more long-term studies need to be conducted to determine the chronic effects of hypoglycemia (when present) on brain physiology and function.

In addition to the ketogenic diet, the patient discussed in this current report ingested alcohol prior to her presentation with hypoglycemia. A hypothesis for how alcohol consumption may have worsened her hypoglycemia could be based on the physiological metabolism of alcohol. In normal alcohol metabolism, the ingested ethanol is oxidized to acetaldehyde and then to acetic acid with the enzyme alcohol dehydrogenase, and nicotinamide adenine dinucleotide (NAD⁺) is reduced to NADH. An increased NADH/NAD⁺ ratio has been shown to suppress hepatic gluconeogenesis and reduce free glucose, perpetuating ketogenesis and hypoglycemia [32-34]. One might use the information in this report to counsel patients on the ketogenic diet to avoid alcohol intake, as it might precipitate hypoglycemia.

3. Conclusion

In this case report, we present the case of a 69-year-old female patient who followed a ketogenic diet for a year, associated with significant weight loss, then presented with significant hypoglycemia after ingestion of alcohol. Her hypoglycemia was likely chronic, given that she had nonspecific symptoms of malaise and mental “fogginess.” There are plausible physiologic mechanisms by which the combination of the ketogenic diet and alcohol ingestion may have precipitated this presentation. However, this dietary pattern may have protected the patient from classic symptoms of hypoglycemia. Whether this effect is beneficial or harmful in the long term remains to be elucidated. Further studies into the long-term benefits and harms of the ketogenic diet are needed.

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Additional Information

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