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Case Report
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23-Year-Old with Recurrent Diabetic Ketoacidosis: A Case of Catamenial Hyperglycemia

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Abstract

Diabetic ketoacidosis is a medical emergency with somatic and psychological implications in patients with type 1 diabetes mellitus (DM1). Menstrual cycle-related glycemic change is rarely described as a precipitant of diabetic ketoacidosis. We present a case of a 23-year-old female with a history of DM1, on her second day of menstruation, who presents with diabetic ketoacidosis. In absence of other precipitating factors, examination of the time pattern of her recurrent diabetic ketoacidosis was consistent with catamenial diabetic ketoacidosis. To date, the reports of catamenial diabetic ketoacidosis are few and without consistent results. Moreover, most of the reports investigated only women with tight glycemic control. Systematic studies of catamenial hyperglycemia suggest variation in hyperglycemic patterns among individuals and even inconsistent glycemic variability patterns with consecutive cycles, making the management of catamenial hyperglycemia challenging. This case illustrates recurrent adverse outcomes (including diabetic ketoacidosis) due to complexities in DM1 management influenced by catamenial hyperglycemia. The complexity of diabetes management suggests the need of closed-loop glucose control systems that self-adjust basal insulin patterns to respond to the glucose management needs throughout menstrual cycles, which may ultimately prevent the risk for catamenial diabetic ketoacidosis, improve overall glycemic control, and reduce psychological burden of DM1.

Introduction

Diabetic ketoacidosis (DKA) is a medical emergency with somatic and psychological implications in patients with type 1 diabetes mellitus (DM1). Several factors can precipitate DKA including serious infection, trauma, cardiovascular diseases and missed insulin doses [1]. In some occasions however, the inciting factor of DKA remains unidentified.

The term "catamenial" (from Greek word "katamenios", meaning "monthly"), refers to monthly menstrual periods [1]. Catamenial hyperglycemia is used to describe increase in blood glucose concentrations related to menstrual cycle phase changes [1,2]. While no standard methods are available for the diagnosis of catamenial hyperglycemia, frequent self-monitoring of blood glucose levels, keeping of a menstrual calendar, in conjunction with a diabetic care team to determine cycle phase variations have been suggested [1,3]. Catamenial glycemic variation has been studied mostly in women who are able to achieve target A1c range. The primary objective of this report is to present a case of uncontrolled DM1 that illustrates recurrent DKA related to catamenial glycemic variation, and highlights the necessity to facilitate glycemic management beyond the standard finger-stick glucose monitoring and multi-dose insulin injection therapy.

Case Report

We present a case of a 23-year-old hispanic female with DM1 and recurrent hospitalizations for DKA who came in with abdominal pain, nausea and vomiting for 1 day. She was diagnosed with diabetes at age 11 her latest hemoglobin A1c was 10.2%, and she had 13 hospitalizations within the last 3 years for recurrent DKA, with rare hypoglycemic events. She reported testing her glucose levels 3-6 times per day, and regularly taking 18 units of glargine every morning as her basal insulin and lispro self-adjusted for prandial and correction doses, as prescribed. The patient reported needing multiple adjustments of her insulin over the course of her menstrual cycle and having poor glycemic control despite intensive self-management without missed insulin doses. She felt discouraged about lack of glycemic control and recurrent DKA despite day-to-day intensive self-management efforts. She was on the second day (early follicular phase – Figure 1) of her menstrual cycle on admission. Physical examination was significant for tachycardia, tachypnea, elevated blood pressure, dry mouth and diffuses abdominal tenderness. Diabetic ketoacidosis was diagnosed based

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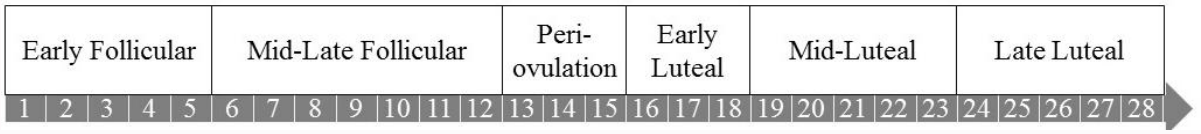

Figure 1: Phases of the 28-day menstrual cycle.

on serum glucose 793 mg/dL, anion-gap metabolic acidosis (anion gap 34, pH 7.16) with high levels of urinary ketones >80 mg/dL and lactic acidosis (24 mg/dL). The work up of precipitating causes for DKA revealed no infectious processes or other inciting events. Examination of the time pattern of her recurrent DKA episodes was consistent with catamenial DKA. The patient was instructed every month at the start of her menstrual period for the 5 days to make the following changes: (1) to increase her insulin doses 10%; (2) use consistent portions of meal carbohydrates; (3) increase frequency of her glucose monitoring (6-8 times per day); and (4) daily contact with diabetes team for insulin dose adjustment. The medical necessity requests for real-time continuous glucose monitoring have not been approved by her insurance provider.

Discussion

Since the first case was described in 1918, only few case reports, small cohort studies, and small prospective investigations of catamenial hyperglycemia and DKA have been published, however without consistent results [1]. The systematic studies of glycemic changes during the menstrual cycle suggests increased risk of hyperglycemia in early luteal phase (days 16-18 of the 28-day menstrual cycle), whereas the risk of hypoglycemia was higher during the follicular phase (days 0-12 of the 28-day menstrual cycle), with the risk of extreme glucose fluctuations increasing during peri-ovulation phase (days 13-15 of the 28-day menstrual cycle) [4]. While mechanisms of menstrual cycle related glucose fluctuations remain elusive [1,2,5], variation in glucose levels has been attributed in literature to insulin sensitivity changes related to menstrual cycle-specific variation in levels of estrogen, progesterone and inflammatory mediators [4,6-8].

The most common pattern of catamenial glycemic variation manifests as hyperglycemia throughout the luteal phase (days 16-28 of the 28-day menstrual cycle), whereas other women manifest hypoglycemia during the late luteal phase (days 24-28 of the 28-day menstrual cycle), presumably due to decreasing estrogen levels during the late luteal phase. According to these reports, luteal hyperglycemia occurs in 58.4% of women, while in 52.2% of women hyperglycemia manifests from the early follicular phase (days 1-5 of the 28-day menstrual cycle) [9], similar to our patient.

Catamenial variation in glycemia is related to variations in insulin sensitivity, and thus glycemic patterns tend to vary among individuals and even within individuals during consecutive menstrual cycles [4,7].

At present, catamenial hyperglycemia remains a diagnosis of exclusion after thorough investigation of other possible causes of hyperglycemia. Diabetic ketoacidosis occurs more often in women than in men, with a female preponderance more evident in the younger population [5]. It is plausible that this gender disparity can be related to catamenial glucose variability in women, if all other precipitants of DKA are accounted for. While no standard methods are currently available for diagnosis of catamenial glucose variability, most experts suggest analysis of menstrual calendar along with day-to- day glycemic variability, in modern days best assessed by continuous glucose monitoring, using consistent carbohydrate intake [1,3].

This case illustrates the complexities of glycemic management related to menstrual cycle in a young woman with DM1. Catamenial hyperglycemia contributes significantly to excess glycemic variability, adding complexity and challenging glycemic management in women of reproductive age. Moreover, as our case illustrates, catamenial hyperglycemia can contribute to poor glycemic outcomes, high A1c, and recurrent hospitalizations due to DKA. Factoring in catamenial factor in management of glycemic variability requires substantial cognitive resources, while these resources may be scarce: extreme glucose variability (acute and recurrent hypoglycemia and hyperglycemia) results in impairment of cognitive reserve (mental flexibility, processing speed, memory, and judgement) and of affective functions (mood swings and anxiety) [10,11]. In certain circumstances, this leads to learned helplessness and subsequent psychological burnout due to feelings of ineffectiveness and lack of accomplishment. Catamenial changes in glycemia add additional unpredictability in day-to-day glycemic control. As the presented case illustrate, this lack of consistent patterns and complexity of glycemic management results in poor glycemic control and recurrent DKA even in motivated patients. Thus, to break this vicious cycle and to address complexities of glycemic management of DM1 the logical future solution is to engage machine learning and artificial intelligence, facilitated by continuous real-time glucose monitoring, and development of closed-loop glucose management systems for women of childbearing age [12].

A meta-analysis [13] and several randomized clinical trials of DM1 management (including the DIAMOND [14], and the GOLD [15] trials), showed a significantly greater improvement in A1c and reduction in hypoglycemia exposure using continuous glucose monitoring compared to conventional finger-stick glucose self-monitoring methods. Regretfully, continuous glucose monitoring too often is not considered a medical necessity by some medical benefit management plans, and thus inaccessible to young women.

There is an overwhelming potential for a closed-loop glucose control systems, which consists of a continuous glucose monitor, a control algorithm, and an insulin pump to guide adjusted insulin dosing, from the simpler application of hypoglycemia prevention or overnight glucose control to the more complex approach of having round the clock glucose control [4]. Lack of consistent patterns in catamenial insulin sensitivity underscores the importance of such closed loop systems to facilitate DM1 management in women of childbearing age. It is highly likely that appropriate closed loop system with algorithms facilitated by machine learning and artificial intelligence have a potential to reduce psychological and medical burden of diabetes management, and have a potential to be cost-effective from the individual, social and financial standpoint by reducing recurrent hospitalizations due to diabetic emergencies [16,17].

Conclusions

Tantamount to treating the acute episode of DKA is identifying and managing the precipitating cause. In cases of DKA with no clear cause, the phase of menstrual cycle as an inciting factor should be considered. This case and review of the available publications suggests the need of closed-loop glucose control systems that self-adjust basal insulin patterns factoring in the glucose management needs throughout menstrual cycles. The use of such glucose control technologies may prove to be effective to prevent the risk of catamenial DKA, improve the overall glycemic control, and reduce psychological burden related to type 1 diabetes in young women.

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