CASE REPORT

Euglycemic diabetic ketoacidosis caused by empagliflozin complicated by failure to thrive in a geriatric patient

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ABSTRACT

Euglycemic diabetic ketoacidosis (euDKA) is a rare but deadly complication of sodium-glucose cotransport-2 (SGLT-2) inhibitors. Primarily indicated for the treatment of Type 2 Diabetes Mellitus, the incidence of euDKA is expected to rise as SGLT-2 inhibitors become a mainstay therapy for diabetics with heart failure. Diagnosis of euDKA can be difficult given the presence of normoglycemia and is especially challenging among geriatric patients that are complicated by additional comorbidities. We present a case of an elderly male with multiple comorbidities who presented for dehydration and altered mentation from a nursing home facility. Laboratory investigations showed signs of acute renal failure, uremia, electrolyte abnormalities, and severe metabolic acidosis due to high levels of plasma beta-hydroxybutyrate. He was admitted to the medical intensive care unit (ICU) for further management. A presumptive diagnosis of euDKA was strongly suspected due to his laboratory data and medication reconciliation which revealed the recent initiation of empagliflozin. The patient was promptly started on a standardized treatment protocol for DKA with continuous infusion of regular insulin with strict glucose monitoring, along with intravenous fluids, and a small dose of sodium bicarbonate infusion as per current standard guidelines. With the rapid improvement in symptoms and metabolic derangements, the diagnosis was confirmed. Geriatric patients from nursing home facilities are a high-risk cohort who if not properly cared for by nursing staff can develop dehydration, malnutrition and worsening frailty including sarcopenia that exposes them to increased risk of medication side effects, such as euDKA. Clinicians should consider euDKA in their differential diagnosis in elderly patients with overt or relative insulinopenia who are receiving SGLT-2 inhibitors when presenting with acute changes in health and mentation.

KEYWORDS: euglycemic diabetic ketoacidosis; SGLT-2 inhibitor; empagliflozin; geriatrics; Jardiance; failure to thrive

INTRODUCTION

Sodium-glucose cotransporter-2 (SGLT-2) inhibitors are oral antihyperglycemic agents used to lower blood sugar in adults with Type 2 Diabetes Mellitus (T2DM) [1]. This class of drug inhibits the action of the SGLT-2 protein that is responsible for the reabsorption of glucose in the kidneys. The first SGLT-2 inhibitor, canagliflozin, was approved by the US Food and Drug Administration (FDA) in March 2013 for the treatment of T2DM [1]. Since then, several other SGLT-2 inhibitors have been approved for use, including dapagliflozin, empagliflozin, and ertugliflozin. According to the American Diabetes Association 2023 guidelines, SGLT-2 inhibitors, are second-line pharmacological agents for adults with T2DM, specifically in those with chronic kidney disease, cardiovascular disease, or heart failure [2,3].

The FDA approved empagliflozin in February 2022 to be prescribed for adults with heart failure with reduced ejection fraction (HFrEF) based largely on the results from both the EMPEROR-Preserved and EMPEROR-Reduced trials that showed a significant reduction in risk of cardiovascular death and hospitalization in this population cohort [4,5]. Consequently, as SGLT-2 inhibitors become a mainstay of contemporary guideline-directed medical therapy (GDMT) and as the medication becomes more affordable, its popularity among prescribers will continue to grow. Currently, the incidence of euDKA in patients treated with SGLT-2 inhibitors varies between 0.16 and 0.76 cases per 1000 patients per year [6]. As such, despite its rarity clinicians should be aware of euDKA as a potential side effect of SGLT-2 inhibitor use.

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Among the many known adverse side effects of SGLT-2 inhibitors, including increased risk for urinary tract infections, dehydration, bone fractures, and sarcopenia, euglycemic diabetic ketoacidosis (euDKA) is a rare but potentially life-threatening condition that occurs in individuals with diabetes [2,6]. While DKA is classically characterized by the triad of high anion gap metabolic acidosis (HAGMA), ketonemia or ketonuria, and hyperglycemia, euDKA is a diagnostic challenge as patients present with normal blood glucose levels and can be often overlooked on the differential diagnosis (Table 1). Other than SGLT-2 inhibitors, the other causes of euDKA include pregnancy, fasting, bariatric surgery, gastroparesis, insulin pump failure, cocaine intoxication, chronic liver disease, glycogen storage disease, lactic acidosis, and starvation ketosis [1,7]. However, in diabetics who take SGLT-2 inhibitors the risk of developing euDKA increases seven-fold [7]. Regardless of the etiology, failure to recognize euDKA early may delay diagnosis and treatment causing worse outcomes and prolonged hospitalizations.

Among geriatrics patients, euDKA can be challenging to diagnose due to complications of sepsis, polypharmacy, cognitive impairment, and frailty [6,7]. Within this context, we report a case of an elderly male with multiple comorbidities who presented from a nursing home with signs of dehydration, altered mentation, and multi-organ dysfunction in which he was admitted to the ICU for acute renal failure, uremia, and euDKA due to recent initiation of SGLT-2 inhibitor therapy.

CASE PRESENTATION

A 74-year-old male with a history of T2DM, hypertension, ischemic stroke, peripheral arterial disease, bilateral non-obstructive renal artery stenosis, chronic right internal carotid artery occlusion, seizures, and vascular dementia presented to the Emergency Department (ED) from a local nursing home due to decreased oral intake and dehydration for at least the past week. Per emergency medical services, the patient's initial blood pressure was 94/49 mmHg en route to the hospital, and was promptly resuscitated with 1 liter of normal saline administered intravenously. Upon arrival, the patient was oriented to self only and somnolent appearing with a blood pressure of 101/59 mmHg, pulse rate of 105 bpm, respiratory rate of 17, 100% oxygen saturation on ambient air, and 37.1 °C temperature. His physical examination revealed a sarcopenic-appearing male with dry mucous membranes but was otherwise in no acute distress. Initial laboratory data was consistent with acute renal failure (ARF), uremia, several electrolyte abnormalities, and severe metabolic acidosis (Table 2). While in the ED, an indwelling urinary catheter was placed, and the patient was noted to be oliguric. An initial urinalysis appeared contaminated, and a repeat test revealed trace amounts of ketones. With growing concern for ketoacidosis, a beta-hydroxybutyrate (BHB) level was ordered that was elevated (31.5 mmol/L). Of note, cardiac diagnostics included elevated but stable high-sensitivity troponin levels measuring 213 ng/L at baseline, with subsequent levels of 223 ng/L and 193 ng/L at 1 and 3 hours, respectively. An electrocardiogram showed normal sinus rhythm without any ST-T changes. In the setting of an initial blood glucose presentation of 180 mg/dL, a presumptive diagnosis of euDKA was suspected. The patient was admitted to the medical ICU for further management and was immediately started on our institution's standardized treatment protocol for the management of DKA with continuous infusion of regular insulin at rate of 5.46 units/hour, along with 100 mEq of sodium bicarbonate to replace his bicarbonate deficit (405 mEq) due to the severity of the metabolic acidosis as per current standard guidelines. Because the risk of hypoglycemia is higher, communication with nursing staff about close monitoring of blood glucose levels and anticipation to administer intravenous dextrose if needed were conveyed. Over the next 48 hours, his anion gap closed as his infusion rate was decreased to 2.73 units/hour followed by 1.59 units/hour and was then concurrently transitioned to subcutaneous insulin and started back on an oral diet (Figure 1). As his laboratory parameters continued to improve his mentation also significantly recovered as he became more alert and oriented. Further, a medication reconciliation revealed a diabetes regimen of both insulin glargine 18 units nightly and insulin aspart 5 units thrice daily before meals as well as recent initiation of empagliflozin once daily one month before. After two days the patient was transferred to the progressive unit and returned to the nursing home a week later. At the time of discharge, his appetite had improved, vital signs and lab parameters returned to baseline, and, importantly, his empagliflozin was discontinued from his active medications while resuming both oral metformin and subcutaneous insulin instead.

Table 1. Parameters and references comparing DKA and euDKA

Laboratory Values for DKA and euDKA			
Measurement	**Reference**	**DKA**	**euDKA**
Blood glucose (mg/dL)	80-130	> 250	< 250
Arterial pH	7.35-7.45	< 7.3	< 7.3
Serum bicarbonate (mEq/L)	22-26	< 18	< 18
Urine ketones	N/A	Present	Present
Serum ketones	N/A	Present	Present
Anion Gap (mEq/L)	0	10-12	10-12

Table 2. Initial laboratory investigations.

Parameter	Reference	Admission
Sodium (mEq/L)	135-145	145
Potassium (mEq/L)	3.5-5	6.6
Blood urea nitrogen (mg/dL)	6-22	207
Creatinine (mg/dL)	06.-1.2	10.20 (baseline 1.10)
Glucose (mg/dL)	70-100	185
Calcium (mg/dL)	8.5-10.5	8.9
Chloride (mEq/L)	95-105	106
Bicarbonate (mEq/L)	22-26	8
Anion Gap (mEq/L)	10-12	31
Venous pH	7.34-7.36	7.09
Lactic acid (mmol/L)	0.7-2.7	4.4

DISCUSSION

Geriatric patients that present to the ICU often have multiple comorbidities that require immediate attention and closer monitoring. As for our patient, he was treated for ARF, uremia, severe metabolic acidosis, demand ischemia, and euDKA. In the initial evaluation, it is easy for clinicians to overlook the diagnosis of euDKA, and for our patient with his clinical signs of failure to thrive the differential diagnosis initially included starvation ketosis. The elevated lactate

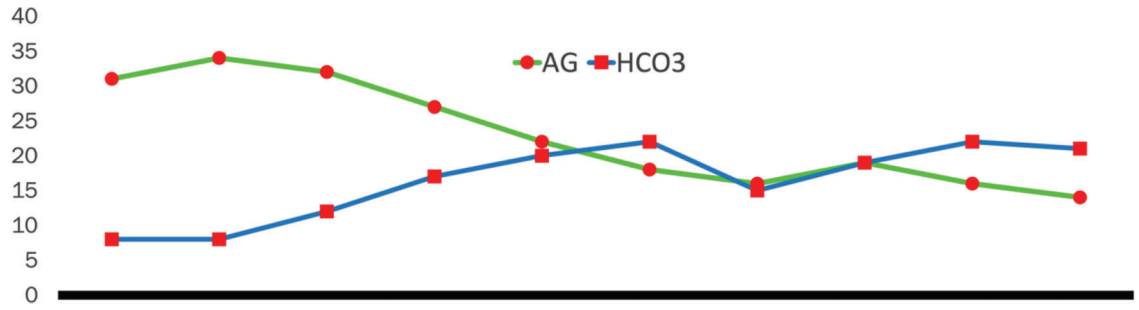

Fig. 1. Trends for both anion gap and HCO3- over the first 48 hours.

could be explained due to metformin the patient had been receiving, however, the severe acidosis and altered mentation initially observed on presentation was unlikely to be solely due to lactic acidosis as severe lactic acidosis carries a very high mortality risk. Indeed, euDKA is usually a diagnosis of exclusion and as our team continued to narrow its differential diagnosis for the initial altered mentation, we believed the association between recent SGLT-2 inhibitor use and his presentation was linked. Mechanistically speaking, SGLT2 inhibitors work in an insulin-independent manner by blocking the reabsorption of sodium and glucose in the kidneys therefore themselves cannot cause insulinopenia. Indeed, patients at risk of developing euDKA usually have a form of underlying insulinopenia (T1DM, T2DM, or pre-diabetes) in addition to other factors that will be discussed shortly.

In hospitalized patients, the presence of euDKA has been associated with prolonged hospital stays though without worsening the risk of mortality [8,9]. The Society of Hospital Medicine highlights certain high-risk presentations, including sepsis and hypovolemia, of which our patient was severely dehydrated. In another case report, authors detailed a 50-year-old patient with a history of arterial hypertension, dyslipidemia, left-side breast cancer which required chemotherapy, radiation therapy and surgery, hypothyroidism, and T2DM that was admitted to the ICU for sepsis, ARF, and severe metabolic acidosis with an AG of 32 [10]. A follow-up ketonemia test was positive and with forehand knowledge of chronic dapagliflozin, the patient was additionally diagnosed with euDKA and treated accordingly. Like our case, elevated levels of urea and creatinine in the setting of ARF and uremia can lead to a decrease in the serum glucose levels which can mask the underlying euDKA. Additionally, the symptoms of euDKA, such as nausea, vomiting, and abdominal pain, can overlap with the symptoms of ARF and uremia, making it difficult to differentiate between the two conditions. Therefore, clinicians should maintain a high index of suspicion for euglycemic DKA in patients with insulinopenia, particularly those with ARF and uremia, who present with unexplained metabolic acidosis, even if the serum glucose levels are not significantly elevated. Serum ketone measurements should be performed in such cases to aid in the diagnosis of euDKA. In another instance, a 69-year-old male was transferred from the general surgery service to the ICU for persistent metabolic acidosis and developing confusion [11]. His laboratory investigations showed normoglycemia but elevated blood ketones, but upon medication review, it was suspected the patient was suffering from euDKA secondary to dapagliflozin use. He was started on the institution's DKA protocol, and his confusion was subsequently resolved. In this case, the patient continued taking his SGLT-2 inhibitor before the endoscopic procedure which likely precipitated his presentation. Major surgical guidelines recommend that patients stop their SGLT2-inhibitors 3 to 4 days before surgery to minimize the risk of postoperative ketoacidosis and urinary tract infections which was ignored in this case [11]. Regardless of the precipitant, clinicians should be mindful that the management of euDKA slightly differs from standardized DKA protocols simply due to the pharmacokinetics of SGLT-2 inhibitors. The medication has a half-life of 13 hours and therefore the associated ketoacidosis may continue for longer than expected [1, 2]. Accordingly, intravenous fluids should be given to replace salt and water losses caused by osmotic diuresis from the increased urinary elimination of sodium and glucose due to SGLT-2 inhibition [10,11].

Within the geriatric population, there remain continued diagnostic challenges toward prompt identification of DKA and even more so euDKA. Of the common comorbidities associated with delayed diagnosis of DKA, sepsis, ARF, cognitive impairment, atypical presentations, and polypharmacy have the potential to mask and confound underlying diagnosis and management of euDKA [12]. As for our patient, two necessary mechanisms that triggered his presentation involved dehydration and insulinopenia [13]. The patient's dehydration was likely exacerbated by his elderly age, dementia, and likely inadequate quality of care provided by his nursing home facility [14,15]. In most patients, SGLT-2 inhibitors do not cause clinically significant dehydration as the thirst mechanism is intact, but geriatrics, especially those with dementia can have an impaired thirst mechanism. Additionally, when nursing home staffing is inadequate and supervision is poor, nursing home residents with severe cognitive and functional impairment and a lack of family or friends to assist them at mealtime are at great risk for dehydration [14]. Our patient reportedly had been withdrawn socially for the past week and had skipped many meals yet nursing still provided his medications independent of his oral intake. Whether they be assisted living facilities, skilled nursing facilities, or long-term care facilities, the major challenges towards providing optimal care range from inability to provide regular glucose monitoring and insulin injections, inadequate staff education, irregular meal intake, high staff turnover, and variation in practitioner management and visitation frequency [15]. Previous data suggests as many as 20% of residents experienced some form of malnutrition that manifested due to depression, cognitive impairment, functional impairment, and swallowing difficulty [16]. Given our patient's sarcopenic appearance, he not only was likely experiencing inadequate nutrition but was likely intrinsically insulinopenic as well. Indeed, the

association between SGLT-2 inhibitors and euDKA arises from the relative deprivation of glucose that leads the body using stored lipids as an energy source, i.e., ketone bodies. However, this pro-ketosis state is considered self-limited and is unlikely to develop into euDKA. However, the clinically apparent malnutrition and geriatric frailty by our patients was exacerbating his underlying physiological insulinopenia therefore contributing to the development of full-blown euDKA. Currently, there are no professional guidelines and guidance on stopping SGLT-2 inhibitor use in the setting of decreased oral intake, altered mentation, or frailty. Future research directions should focus on risk factors among geriatric patients with either diabetes or heart failure that correlate with the development of euDKA. Thus, within this context, geriatric individuals living at nursing homes who take SGLT-2 inhibitors may be at increased risk of developing euDKA if they are inadequately cared for and monitored. Further large-scale observational studies are needed to further elucidate the relationship between SGLT-2 inhibitors and euDKA.

CONCLUSIONS

Our patient presented with profound hypotension and multi-organ dysfunction in the form of ARF and myocardial injury that was complicated by euDKA. The demand ischemia with raised cardiac biomarkers due to severe volume contraction and metabolic acidosis responded well to fluid resuscitation and insulin infusion. The risk of overt euDKA development increases when the pro-ketosis state induced by SGLT-2 inhibitors combines with existing insulinopenia in individuals such as those with T2DM. Of the usual triggers for euDKA, our patient's health had deteriorated due to inadequate nutrition and hydration complicated by geriatric frailty that worsened his underlying insulinopenic state. Indeed, management of euDKA is essentially the same as that of DKA except dextrose infusion is often aggressively initiated immediately. A favorable prognosis depends on early recognition and screening with serum or urine ketones, even when serum glucose is normal. In the ICU setting, geriatric patients with euDKA can be particularly difficult to diagnose or even simply be overlooked altogether while receiving complex medical interventions for multiple comorbidities. In sum, while a diagnosis of exclusion, clinicians should have a high index of suspicion for euDKA in patients with normal blood glucose levels and HAGMA in the setting of SGLT-2 inhibitor use, and even particularly so among geriatrics with dementia presenting from nursing homes that have multiple comorbidities and variable quality of care.

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Informed consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

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