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Master thesis | Original study

Life-threatening euglycemic ketoacidosis in pregnancy: A case report with narrative review of the literature

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Abstract

Euglycemic ketoacidosis (EKA) is a serious but infrequent condition in patients with or without diabetes. It usually follows a period of severe vomiting, illness, or starvation. The condition can be difficult to diagnose due to misleading euglycemia and a wide range of possible, nonspecific symptoms. We report a case of a 41 years old pregnant woman, with an hitherto undiagnosed COVID infection, and admitted with EKA. Along with the case presentation, we discuss the pathophysiology, typical risk factors (including pregnancy, infection, low calorie intake), symptoms, diagnosis, treatment and overall management of EKA.

Keywords: **Euglycemic ketoacidosis, pregnancy, ketones measurement, COVID-19.**

Introduction

Euglycemic ketoacidosis (EKA) is an acute life-threatening metabolic
emergency characterized by ketosis, raised anion gap metabolic acidosis and normal blood glucose levels[1]. EKA needs to be recognised as early as possible, despite the diagnosis can be challenging due to misleading euglycemia and a wide range of unspecific symptoms. Treatment delay has been associated with worse outcome and can have deleterious effects on maternal and fetal health during pregnancy. While covid-19 infection is frequently associated with ketoacidosis, data about pregnancy-related euglycemic ketoacidosis with concomitant Covid-19 are rare[2].

The main objective is to make physicians aware of the diagnosis of EKA, as it is a life-threatening condition which can easily be missed. We therefore present a case report plus narrative review in which we discuss the available evidence regarding the pathophysiology, typical risk factors (including pregnancy, infection, low calorie intake, COVID infection), symptoms, diagnosis, treatment and overall management of EKA.

Case presentation

FA 41-year-old woman (G4P3M3) presented at the emergency department at 30 weeks of gestation with a 6-day history of dyspnea and anorexia. She had no relevant past medical history. Gestational diabetes had been excluded by means of a non-fasting Oral Glucose Tolerance Test in the past weeks before admission of the patient. On admission she was lethargic, tachycardic and tachypnoeic with a respiratory rate of 35/min and a peripheral oxygen saturation of 94% while receiving 5l/min oxygen via a non-rebreather mask. She had no specific digestive symptoms. Initial arterial blood gas illustrated a raised anion gap metabolic acidosis: pH 7.25, pCO2 16.9mmHg, bicarbonate 8.1mmol/l, sodium 132mmol/l, chloride 97 mmol/l, base excess 17.4mmol/l, lactate 0.8mmol/l, glucose 150mg/dl and PaO2 143 mmHg with FiO2 of 40%. Urinary ketones measured 4+. CRP was 45mg/l and Covid-PCR was positive with a high viral load. An urinary infection was excluded. Given the absence of elevation of her blood pressure compared with outpatient values, the diagnosis of preeclampsia was refuted despite a mild proteinuria. Fetal movement and heart

rate were normal. She was diagnosed with EKA and received fluid resuscitation with electrolyte replacement in combination with intravenous 10% dextrose and insulin infusion. After 2 days the supplementary oxygen was stopped and after 3 days the patient could leave the intensive care unit.

Methods

Given limited data, our study included any peer-reviewed studies, including case reports. We searched the PubMed and MEDLINE database using the following keywords: 'euglycemic ketoacidosis', 'euglycemic diabetic ketoacidosis' and 'ketones measurement'. Secondary searches included reference list checking of the included articles, electronic searches for included interventions by name and author, and citation tracking of all included articles. A review of the abstract of each retrieved study was then carried out. Only publications with abstract and/or full text in English language of the past 10 years were included. Figure 1 shows the process of identification, screening and exclusion of the retrieved articles. This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement (Figure 1)[3].

Results

A total of 211 articles were identified, 188 from initial searches, and 23 from secondary searches. After duplicates were removed, the titles and abstracts of 183 articles were screened. Of these, 46 full-text articles met the initial criteria and were retrieved for review, with 31 studies meeting the final inclusion criteria. The flow of studies, and reasons for exclusion at each stage, is summarized in a PRISMA diagram (Figure 1).

Pathophysiology

Euglycemic ketoacidosis (EKA) is an acute life-threatening metabolic emergency characterized by euglycemia (blood glucose levels less than 200 mg/dl) with metabolic acidosis (arterial pH less than 7.3, serum bicarbonate less than 18 mmol/l) and ketonemia.

The underlying mechanism is based on a general state of starvation, resulting in ketosis while maintaining normoglycemia. Conditions like

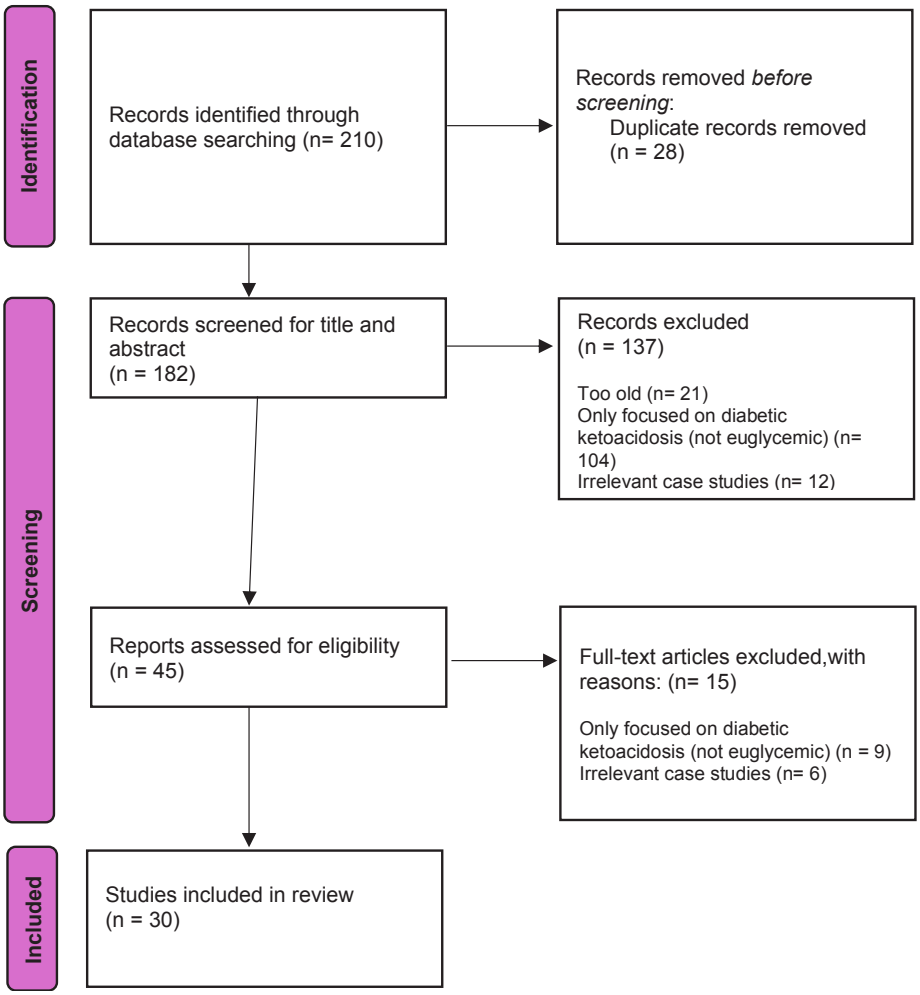

Fig. 1 — Process of identification, screening and exclusion of the retrieved articles.

anorexia, gastroparesis, fasting, use of a ketogenic diet and alcohol abuse disorder can lead to states of carbohydrate starvation and resultant ketosis. This carbohydrate deficit results in generalized decreased serum insulin and excess counter-regulatory hormones like glucagon, epinephrine, and cortisol. The increased glucagon/insulin ratio leads to increased lipolysis, increased free fatty acids and ketoacidosis[4].

Ketone body production in EKA is similar to diabetic ketoacidosis (DKA) with acetoacetic acid, beta-hydroxybutyric acid (after acetoacetic acid reduction) and acetone (after acetoacetic acid decarboxylation) being the major metabolites (Figure 2). The resulting raised anion gap metabolic acidosis triggers respiratory compensation and sensation of dyspnea as well as nausea, anorexia, and vomiting. Volume depletion, resulting from decreased oral intake and vomiting further exacerbates elevations in glucagon, cortisol and epinephrine. The increase in these counter-regulatory hormones then further worsens lipolysis and ketogenesis. Additionally, decreased gluconeogenesis in the liver occurs during fasting when hepatic glycogen is already depleted, may enhance EKA. Increased glucosuria by the kidneys may also contribute to EKA[5-7].

Risk factors

Risk factors for the development of EKA include pregnancy, pancreatitis, glycogen storage disorders, surgery, infection, cocaine toxicity, cirrhosis, COVID-19 infection, insulin pump use and the use of sodium-glucose cotransporter 2 (SGLT2) inhibitors[8-10]. Patients taking SGLT2 inhibitors should have these medications discontinued as soon as the diagnosis is recognized.

Pregnancy is a risk factor for EKA because of the physiologic state of hypo-insulinaemia and increased starvation. This predisposition occurs through multiple mechanisms with the first mechanism being marked insulin resistance during pregnancy caused by several hormones including human placental lactogen, placental insulinase and progesterone. These hormones are peaking in the second and third trimesters of pregnancy and can inhibit the effects of maternal insulin, resulting in relative insulin deficiency. This could explain why EKA is most commonly seen during the second and third trimester[11-13].

EKA during pregnancy is associated with multiple immediate and late foetal complications[12]. Maternal EKA can increase the rate of foetal mortality because of decreased uterine perfusion (up to 9%), foetal hypoxia and recurrent late decelerations[7].
The fetal effects of EKA arise from a combination of severe maternal dehydration and acidosis which may reduce uteroplacental perfusion. Maternal electrolyte imbalances may result in fetal cardiac arrhythmias and risk of fetal cardiorespiratory arrest. Although there are no studies that show the

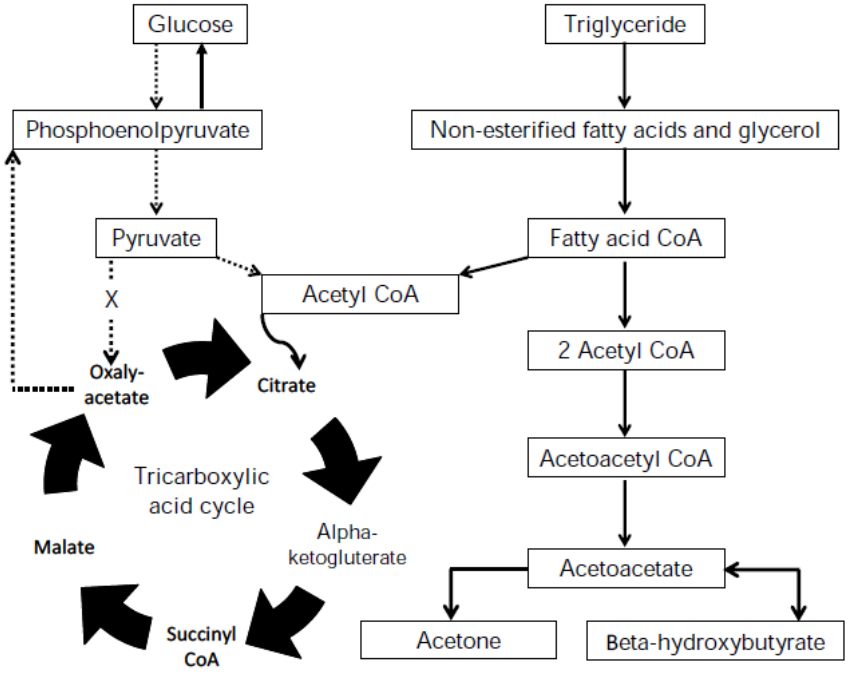

Fig. 2 — A simplified illustration showing the metabolic pathway for ketogenesis. During insulin deficiency, glucose uptake into cells is limited, and there is a need for an alternative energy substrate. The breakdown of non-esterified fatty acids allows the entry of fatty acid CoA to enter the tricarboxylic acid cycle, thus generating ATP. However, excess fatty acid CoA production leads to the production of acetoacetate (a ketoacid) and beta-hydroxybutyrate (a hydroxyl-acid), causing ketoacidosis in periods of extended insulin deficiency(25). This figure is from Dhatariya et al, 2016.

long-term consequences for the fetuses born alive, neurodevelopmental alterations with impaired brain development have been observed[11]. The necessary frequency of fetal monitoring is unknown and no definite recommendations are currently available. Therefore, individualized care relying on a multidisciplinary approach is recommended. The decision to deliver should be individualized and based on the evaluation of the maternal clinical status, laboratory results, fetal gestational age, cardiotocography, and ultrasound.

Immediate delivery is not always automatically indicated unless there is no improvement in CTG despite correct treatment suggesting emergency caesarean delivery is necessary[14]. In our patient, the CTG remained normal, most probably because of the prompt detection and correction of maternal ketoacidosis. The patient later had a normal vaginal delivery.

The relative hypoglycaemic state seen during pregnancy causes the body to increase lipolysis as a fuel source for the pregnant mother. This results in a concomitant increase in ketone formation via ketogenesis using the products of fat breakdown. In the setting of stressors such as severe vomiting, fasting or infection, ketogenesis may become even further accelerated. This predisposes women to the development of ketoacidosis[13,15].

COVID-19 infection increases insulin demand and predisposes to gastrointestinal symptoms, such as diarrhoea, nausea, and anorexia, leading to volume depletion and increased fat breakdown, thus resulting in increased ketone bodies production[14,16-18]. The mechanism is not fully understood but might be attributed to the interaction of the COVID-19 virus with the angiotensin-converting enzyme II (ACE2) receptor. This receptor is expressed in the pancreatic islets, vascular endothelium, and adipose tissue. The binding of the virus to the ACE2 receptor on pancreatic beta cells facilitates entry into the cells and may induce inflammation that contributes to the destruction of beta cells and their ability to produce or respond to insulin. In this situation, COVID-19 infection may create an environment of pseudo-starvation leading to increased lipolysis, ketogenesis, and ultimately ketoacidosis[2,5]. We believe that the COVID-19 infection in this patient was an interesting but accidental finding. The patient was tachypneic and admitted with supplementary oxygen, but after correct treatment for EKA after 2 days the supplementary oxygen was stopped.

SGLT-2 inhibitors are the latest group of medications added to the arsenal to treat patients with diabetes mellitus. Their promotion in type 2 diabetes mellitus is because of protection against major adverse cardiovascular events and reduced hospitalization for heart failure and death. SGLT2 inhibitors are also associated with a slower rate of decline in the estimated GFR with a lower risk of serious renal outcomes. This makes them an excellent choice for patients with diabetes and cardiovascular disease. SGLT2 inhibitors act by blocking the SGLT-2 cotransporter, located in the early proximal renal tubule, which is responsible for the reabsorption of most of the glucose filtered by the glomerulus. It leads to glucosuria and resultant lowering of blood plasma glucose concentration. The exact mechanism that can precipitate EKA in susceptible individuals includes osmotic diuresis along with glucosuria (causing a state of carbohydrate deficit), volume depletion and dehydration. Carbohydrate deficit and hypovolemia promote glucagon release, increase glucagon/insulin ratio and trigger ketogenesis with euglycemia. The other factors include the direct effect of SGLT-2 inhibitors on pancreatic alpha cells, causing glucagon release and inhibiting ketone bodies excretion by the kidneys. Any other precipitants like increased insulin resistance due to stress or extended fasting could transform the patient from this drug-induced ketogenic state to ketoacidosis[19,20].

Symptoms

Signs and symptoms of EKA will vary on a case-by-case basis but closely resemble a hyperglycaemic DKA presentation, although perhaps without polyuria and polydipsia. EKA patients can present with nausea, vomiting, shortness of breath, generalized malaise, lethargy, loss of appetite, fatigue, abdominal pain and can have deep, rapid breathing known as Kussmaul respiration. This represents the respiratory compensation for severe metabolic acidosis. They may have a fruity odour of their breath because of the loss of acetone. Tachycardia, hypotension, altered mentation, increased skin turgor and delayed capillary refill are all signs of total body fluid losses. In severe cases, severe dehydration and metabolic derangement can lead to hypovolemic shock, lethargy, respiratory failure, coma and death.

The onset of EKA can be more insidious compared to hyperglycemic DKA because of the mechanism of subacute starvation that is required to induce ketosis and dehydration. An ill-feeling patient with symptoms such as malaise, dyspnea, nausea, or vomiting should undergo screening with serum pH and blood or urine ketone testing.

Diagnosis

The initial laboratory evaluation of patients suspected to have EKA includes basic electrolytes, glucose, calcium, magnesium, creatinine, BUN,

serum or urine ketones, arterial or venous blood gas analysis, lactic acid and electrocardiogram. Urine screening for ketones with nitroprusside reagent does not measure beta-hydroxybutyrate but does detect acetone and acetoacetate. Serum levels of beta-hydroxybutyrate are typically greater than 3 mmol/l in EKA (normal values less than 0.5 mmol/l). Serum osmolality, to assess for an osmolar gap, and toxic alcohols should be measured to rule out toxic alcohol ingestion when suspected in any patient with severe, unexplained anion gap metabolic acidosis. Close attention should be paid to the anion gap to help direct diagnosis, workup and management.

It is important to know the limitations of measurement of blood and urine ketones (shown in Figure 3). The urine ketone stick test is a relatively cheap method of detection that, unlike plasma ketone measurement, requires no special equipment and does not require any training to use. The urine test uses a nitroprusside reaction and gives a semi-quantitative measure of acetoacetate. However, this test does not detect β-hydroxybutyrate, which is the predominant metabolite present in EKA. Because of the imbalance between the concentration of acetone and β-hydroxybutyrate, the quantity of ketones measured in the urine does not equate the plasma ketone concentration. Therefore it is possible for the urine testing to be negative although the patient has elevated ketones.

Patients with EKA are also dehydrated and consequently have a low urine output. It may take several hours until urine is produced again, which delays treatment unnecessarily. Any estimation of urine ketones collected in this way will be an average of the concentration within the urine held in the bladder since the last void. Interestingly, once treatment has been initiated and acidosis is disappearing, β-hydroxybutyrate is oxidized to acetoacetate causing urine ketone readings to rise even if blood β-hydroxybutyrate concentrations are dropping. This paradoxical rise in urinary acetoacetate would give the false idea that the patient is deteriorating during treatment[21,22].

The value of 3.0 mmol/l for ketone measurement should be used as the cut-off for diagnosing EKA. Urine ketone and capillary testing have sensitivities of 95-100% in diagnosing EKA (using 3.0mmol/l as cut-off). However capillary testing is significantly faster, and has higher specificity (78-94% vs. <50%). Thus, capillary and urine ketone

Plasma ketones		Urine ketones	
Advantage	Disadvantage	Advantage	Disadvantage
Measures the current plasma ketone concentration, allowing diagnostic certainty, and subsequent management plan			Reading is an average of urine ketone concentration since last void; management may be delayed
Allows for timely change of treatment as necessary			Length of time to resolution of DKA may be overestimated
Fast, immediate measurement			Urine sample collection may be delayed due to dehydration
Greater sensitivity and specificity for DKA			Lower sensitivity and specificity for DKA
Measures beta-hydroxybutyrate, the predominant ketone in DKA			Measures only acetoacetic acid, not beta-hydroxybutyrate
	Potentially painful	Painless	
	Equipment (meter) needed	Readings can be read off the bottle	
	Meter needs regular quality assurance testing	No quality assurance needed	
	Staff who is able to use the meter required (if in hospital)	No technical skill required to use the equipment	
Individually wrapped ketone strips have a long shelf life			Ketone strips have a relatively short shelf life
	Relatively expensive	Relatively cheap	
	Meter may be inaccurate at readings outside the range it is designed for		
	Interference caused by other substances (e.g. vitamin C), giving inaccurate results		Interference caused by other substances (e.g. vitamin C), giving inaccurate results

Fig. 3 — Comparison of the advantages and disadvantages of ketone measurement methods(25). This figure is from Dhatariya et al, 2016.

concentrations are both excellent in ruling out EKA. The use of capillary ketones has the advantage of sparing unnecessary time and expensive laboratory investigation because their use is likely to reduce the number of false positive results[23,24].

Because of a possible large variation at high ketone concentrations, bedside ketone meters should only be used to assess the efficacy of the treatment and to make sure that ketone concentrations are decreasing rather than to judge the severity of ketoacidosis. Although ketone concentrations should decrease by 0.5 mmol/l/hr, at high ketone concentrations the large coefficient of variation may make more accurate measurements difficult. However, from a clinical and practical perspective, ketone reduction considerations should be taken into account, in combination with the other biochemical and physical findings and the underlying cause when treating a patient with EKA[25-27].

As described previously, the patient will have normoglycemia (capillary blood glucose less than 200 mg/dL) in the presence of metabolic acidosis (pH less than 7.3) and a total decreased serum bicarbonate (less than 18 mmol/l). Ketones are elevated although urine testing could be false negative. Lactic acid may be elevated but should not account entirely for the elevation in the anion gap. Leukocytosis may be present in the case of a concurrent infection; however, it is nonspecific and could also be due to haemoconcentration or stress, among other causes. Potassium levels will vary but great attention should be paid to the level before starting therapy, as total body potassium is usually depleted. Hypomagnesemia and hypophosphatemia can be seen in the starvation state due to decreased total intake and increased losses. Mild hyponatremia may also be seen but is generally less severe than the pseudo-hyponatremia seen in profound hyperglycaemic states[28].

Treatment

Treatment is multimodal. Obviously, the underlying cause, such as infection, needs to be managed and fluid resuscitation should be initiated since patients usually present profoundly dehydrated. Fluid resuscitation should be initiated by the administration of isotonic saline or lactated ringers solution. 1 to 1.5 L/hr isotonic fluids are recommended during the first 1 to 2 hours in the absence of cardiovascular disease, renal impairment or other comorbidities that preclude aggressive fluid replacement. Subsequent fluid replacement depends on the patient's hydration status, serum electrolytes, serum glucose, and urinary output. Continuous insulin infusion should follow fluid replacement, contingent on serum potassium levels greater than 3.3 mmol/l, starting at a rate of 0.05 to 0.1 U/kg/hr[29].

Ketogenesis is strongly inhibited in the presence of insulin. Insulin regulates ketone body metabolism in two different ways. It blocks lipolysis in adipocytes and it promotes glucose uptake and oxidation by tissues. This results in a rise of the intermediates succinyl-CoA and malonyl-CoA levels. These intermediates are strong inhibitors of fatty acid oxidation and ketone body formation in the liver and other ketogenic tissues. When insulin levels are low, the catabolic, counterregulatory hormones glucagon, cortisol, growth hormone, catecholamines, epinephrine, norepinephrine and thyroid hormones are elevated. They all stimulate lipolysis and the release of free fatty acids as well as fatty acid transport to the liver and skeletal muscles. Increased influx of fatty acids to the liver induces their β-oxidation and subsequent ketogenesis. Insulin also has a small stimulatory effect on extrahepatic ketone body utilization[30].

Since serum glucose in EKA is less than 200 mg/dL, in contrast to DKA, dextrose 5% should be added initially to the fluids to avoid hypoglycemia and hasten clearance of ketosis. Consider increasing the amount of insulin and dextrose to 10% if ketoacidosis persists on D5%. Potassium should be carefully monitored as well, as total body potassium levels will likely be depleted, and IV supplementation of potassium and other electrolytes may be needed. Blood glucose levels should be checked hourly and electrolytes every four hours at a minimum, which is also the standard for the treatment of DKA[29].

Sodium bicarbonate infusions are not indicated, and their use is even controversial in the setting of severe acidaemia with pH less than 6.9. Patients will generally require ICU admission for close haemodynamic and laboratory monitoring as well as frequent titration of insulin infusion. Treatment with IV fluid resuscitation should continue until acidosis is normalised and anion gap is closed.

Most patients with EKA recover well with adequate recognition and treatment. Late diagnosis and inadequate treatment, especially involving hydration without dextrose/insulin infusion, can lead to persistent acidosis, vomiting and prolonged hospitalization. Prognosis is worse for small children and pregnant women.

Discussion

EKA is a life-threatening metabolic derangement that can lead to serious complications including significant dehydration, particularly if not recognized early and treated appropriately with fluids, dextrose,

and insulin. It presents a diagnostic challenge for physicians due to the variety of aetiologies, symptoms and normal blood glucose levels.

Diagnosis of EKA can be challenging and delayed treatment is associated with worse outcome. Signs and symptoms of EKA will vary on a case-by-case basis but mostly present with nausea, vomiting, dyspnea, generalized malaise, lethargy, loss of appetite, fatigue and possibly with Kussmaul respiration.

Unfortunately, the interpretation of the available evidence is hampered by a vast heterogeneity of the literature concerning symptomatology, diagnostic management and treatment strategies. Our review is therefore an attempt to give an overview of and to categorize the currently available evidence. We acknowledge that our review suffers from several limitations with especially low quality studies.

In conclusion, clinicians should be aware of EKA as a life-threatening metabolic condition that can be easily overlooked. Studies are warranted to better understand the prevalence, pathophysiology and management of this condition. In addition, future guidelines should consider identifying the optimal time to discontinue SGLT-2 inhibitors prior to a (major) surgery.

To conclude this discussion, we can ask the question if (capillary) ketone testing should be performed more frequently in the emergency department. Especially because of the new SGLT2 inhibitors and its complications stated above in the article. More investigation is necessary to answer this question.

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