Review Article

Euglycemic Diabetic Ketoacidosis: From Basics to Clinical Practice - Review Article

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Euglycemic diabetic ketoacidosis (DKA) is a life-threatening endocrinological emergency characterized differently from its typical counterpart by normalized or slightly elevated plasma levels of glucose, defined as less than 200 mg per dL, which can result in a delay of diagnosis and treatment. This condition can occur in both type 1 and type 2 diabetes mellitus. Common causes of euglycemic DKA include prescription and use of sodium glucose cotransporter-2 inhibitors (SGLT-2i), pregnancy, glycogen storage diseases, diet restriction, starvation, and states of stress such as post-operative states, acute pancreatitis, infections, and intercurrent illnesses. As with DKA, patients with euglycemic DKA also require immediate emergency evaluation and treatments including rapid correction of dehydration along with correction of electrolytes and use of continuous intravenous insulin with a dextrose infusion until the blood glucose is controlled, the wide anion gap metabolic acidosis is resolved, and the ketone values are normalized. This article includes the definition, epidemiology, pathogenesis, diagnosis, differential diagnosis, and management of euglycemic DKA to enlighten clinicians on the awareness of this condition.

Keywords: Euglycemia, Acidosis, Diabetes, Emergency, Sodium glucose co-transportor-2 inhibitors

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Diabetic ketoacidosis (DKA) is a life-threatening endocrinological emergency characterized by a classical clinical triad consisting of hyperglycemia, ketonemia, and metabolic acidosis. DKA mostly occurs in patients diagnosed with type 1 diabetes mellitus (T1D) but may also occur in patients with type 2 diabetes mellitus (T2D) and gestational diabetes mellitus[1]. Patients with DKA typically present with polydipsia, polyuria, dehydration, hyperventilation, abdominal pain, nausea, vomiting, and even an altered mental status[2-4]. In 1973, a new entity called "euglycemic diabetic ketoacidosis" was first introduced by Munro et al in a series of 211 patients presented with episodes of diabetic metabolic decompensation. Thirty-seven patients had severe euglycemic DKA, defined by a blood sugar level of less than 300 mg per dL and plasma bicarbonate of 10 mEq per L or less. All were young and diagnosed with T1D[5].

Euglycemic DKA is characterized by milder degrees of hyperglycemia with blood glucose values often below 200 mg per dL[6]. This poses a challenge in the clinic because blood glucose values of less than 200 mg per dL can be misleading and result in delayed diagnosis and treatment. Euglycemic DKA has been reported in several case reports and case series of patients whom are diagnosed with T2D and prescribed with sodium glucose cotransporter-2 inhibitors (SGLT-2i)[7-11]. However, other causes accompanied with euglycemic DKA have also been noted including pregnancy, sepsis, decreased caloric intake, cocaine abuse, heavy alchohol drinker, pancreatitis, and liver cirrhosis[11,12]. An awareness of these factors is important to prevent delay diagnosis and treatment in patients with DKA. As with DKA, patients with euglycemic DKA also require immediate emergency evaluation and treatment.

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Definition

Hyperglycemia in typical DKA is defined as a serum glucose level more than 200 mg per dL[13] or more than 250 mg per dL[14] according to the Joint British Diabetes Societies or the American Diabetes Association, respectively. Euglycemic DKA, however, differs from typical DKA by normal or slightly elevated plasma glucose levels currently defined as less than 200 mg per dL[6] hence the name "euglycemic". It occurs in the presence of absolute or relative insulin deficiency thus, resulting in DKA. This poses a challenge in making a diagnosis because of its atypical presentation of normal serum glucose levels as well as milder clinical signs and symptoms not typically seen in DKA.

Epidemiology

Although there has not been a study conducted to shine some light on the incidence and outcomes of patients diagnosed with euglycemic DKA in Thailand, many papers have discussed the topic of euglycemic DKA. Once considered as a rare form of DKA, recent studies have suggested that euglycemic DKA might not occur so infrequently after all. Since the introduction of SGLT-2i, an oral hypoglycemic drug used mainly to treat T2D, several case reports and case series have described euglycemic DKA occurring in patients treated with this agent. In a study conducted by Peters et al[8], 13 episodes of DKA associated with mild hyperglycemia or normoglycemia have been reported in 9 individuals being treated with canagliflozin. Seven out of the 9 patients manifested 11 episodes of DKA and all had T1D. The serum glucose levels at the onset of DKA were less than 200 mg per dL in 6 episodes, 200 to 250 mg per dL in 4 episodes, and undetermined in 1 episode. The remaining two individuals in the study had T2D, had undergone surgery either 1 week or 12 hours earlier before onset, and were reported with a plasma glucose of less than 200 mg per dL[8]. Another study by Hine et al[15] reported 2 cases of euglycemic DKA. Both patients had T2D and were prescribed with dapagliflozin. One of the subjects had undergone a distal pancreatectomy for mucinous cystadenoma and was treated with insulin after the surgery, but insulin was later switched to dapagliflozin during the subsequent stay in the intensive care unit (ICU). Within 24 hours after treatment change, the patient developed DKA with a blood glucose level of 106 mg/dL. The second patient also developed DKA with a serum glucose level of 187 mg/dL. However, no direct contributory factor was reported but a history of pancreatitis and pancreatic atrophy was found[15]. A recent systematic review also reported 42 cases of euglycemic DKA occurred perioperatively associated with SGLT-2i identified from 33 publications. Canagliflozin, dapagliflozin, and empagliflozin were implicated in 26, 10, and 10 of these cases, respectively. Precipitating factors of euglycemic DKA were diet modifications and inter current illnesses. Twelve patients with euglycemic DKA had undergone bariatric surgery including 10 patients that had very low-calorie diet regimes as a precipitating factor. However, no precise association between the interruption of SGLT-2i and the occurrence of DKA was identified. Seven patients required mechanical ventilation while acute kidney injury was identified in 5 cases and an additional 5 patients needed imaging to rule out anastomotic leakage and pulmonary embolism with all findings reported negative. The outcomes were only available in 32 cases and all of them had fully recovered from euglycemic DKA without any apparent complications[16].

Pathophysiology of euglycemic diabetic keto-acidosis

In normal individuals, blood sugar levels are maintained in homeostasis by balanced activities of insulin, which primary effects are to lower plasma glucose levels, and counter-regulatory hormones such as glucagon, growth hormone, catecholamines, and glucocorticoids, which act to increase blood sugar levels. If insulin activity was absent while there was increased activities of counter-regulatory hormones, specifically glucagon, DKA developed. In euglycemic DKA however, the mechanism is slightly different. The current mechanism initiating euglycemic DKA is thought to be due to decreased carbohydrate reserve, resulting in insulinopenia or increased secretion of counter-regulatory hormones, which is mainly glucagon. An increase in the glucagon over insulin ratio promotes lipolysis and ketogenesis via the gluconeogenic pathway. Meanwhile, the carbohydrate deficit results in euglycemia. It is already known that the insulin concentration required to inhibit lipolysis is far less than what is needed to promote glucose utilization at insulin dependent tissues, however it is still hard to say what is the trigger of euglycemic DKA. As of the introduction of SGLT-2i, studies on the pathogenesis of SGLT-2i associated euglycemic DKA has cleared an amount of ground on euglycemic DKA[17] and has shown that euglycemic DKA can occur in both T1D and T2D[11,15,18-24]. SGLT-2i are a

group of new oral hypoglycemic agents ending in "-glifozin" and are indicated for use in patients with T2D[22]. These agents act by inhibiting sodium glucose cotransporter-2 located at proximal renal tubules resulting in decreased reabsorption of up to 30% to 50% of glucose[25,26] as well as sodium. This results in glucosuria and thus, decreases serum glucose levels. Following the drop of plasma glucose, insulin release is decreased and as such, increased lipolysis and ketogenesis is expected. Increased reabsorption of ketones also contributes to ketonemia[24]. There have also been studies in humans that have reported that SGLT-2i stimulate pancreatic alpha cells to release glucagon further stimulating ketogenesis[19,21,24]. This overall procress can explain why patients prescribed with SGLT-2i present with euglycemic DKA. Risk factors associated with SGLT-2i induced euglycemic DKA include acute medical illnesses[15,23], surgery[15], low carbohydrate diets[18], insulin withdrawal or dose reductions, latent autoimmune diabetes in adulthood (LADA)[23], poor beta-cell function reserve, and stress[17]. An illuminating part of SGLT-2i associated euglycemic DKA is that it is considered more of a "starvation" than a "diabetic" one, because of the relatively low glucose levels putting the body in a state of relative starvation due to less carbohydrate reserves[17]. The distinction between theses two entities is that euglycemic DKA occurs primarily as a result of severe insulin deficiency rather than pure starvation, as starvation-induced ketosis rarely develops to severe ketoacidosis in a non-insulin-dependent diabetic patient. Interestingly though, some euglycemic DKA have occurred as a result of starvation during the use of SGLT-2i agents[18]. This shows that ketosis can be initiated by either carbohydrate deficit such as fasting or starvation and SGLT-2i use, or by insulin deficiency whether it is absolute or relative. As described before, starvation-induced ketosis rarely develops to severe ketoacidosis in the setting of an insulin independent diabetic patient. However, if other precipitants were introduced such as muscular dystrophy [Duchenne's muscular dystrophy (DMD)][27-29], significant weight loss, chronic liver disease, and glycogen storage disorders, aggravation of glucose deficit occurs due to accelerated glycogen depletion and curtail gluconeogenesis with less substrates and poor liver functional reserve. A metabolic shift from glucose to lipid follows, and eventually the patient ends up with euglycemic DKA. Glycogen storage diseases, particulary type VI also known as "Hers disease" has also been reported as a cause of euglycemic DKA[30]. It is caused by deficiency of liver glycogen phosphorylase due to an autosomal recessive inheritance mutation of the PYGL gene. Glycogen phosphorylase plays a role as a rate-limiting enzyme in glycogenolysis, as such during events of illnessess or stress fasting, hypoglycemia occurs due to relative decrease in glycogen stores. Pregnancy is also associated with euglycemic DKA. In the setting of pregnancy, DKA is considered a serious metabolic complication with high mortality if it remain undetected and will compromised both the mother and fetus. DKA mostly occurs in the second and third trimester because of increased insulin resistance, use of corticosteroids to promote fetal lung maturation, and the use of beta-agonists as tocolytics[12]. DKA in pregnant patients however, occur at a much lower plama glucose concentration because pregnancy is a ketosis-prone state and thus, "euglycemia" develops. This can be explained because in pregnancy there is a relative state of accelerated starvation. The placenta and fetus rely on large amounts of maternal glucose as a main energy source for growth and development of the fetus. This results in a decreased maternal fasting glucose concentration. As described before, because there is a lower maternal plasma glucose concentration, the body compensates by producing more glucose to elevate maternal serum glucose levels[31-33]. This is caused by increased activities of counter-regulatory hormones found in pregnancy such as progesterone, estrogen, human placental lactogen, and TNF-alpha, and results in a state of insulin resistance[32]. When insulin resistance develops, there is increased lipolysis and gluconeogenesis, thus more secretion of free fatty acids and finally ketosis develops, followed by acidosis. In pregnancy, there is an increase of minute ventilation that places the patient in a state of respiratory alkalosis. Therefore, the renal system compensates this alkalotic state by excreting bicarbonate into the urine. This greatly exacerbates acidosis in pregnant patients with DKA because there is less renal buffering capacity[33]. As a conclusion, euglycemic DKA develops due to states of carbohydrate deficits or along with continued administration of insulin contributing to the euglycemic part while acidosis develops as a result of increased ketogenesis. By combining these two processes together, euglycemic DKA eventually develops (Figure 1).

Diagnosis

The Joint British Diabetes Societies has proposed a diagnostic criteria for the diagnosis of DKA based upon laboratory values that define the classical triad

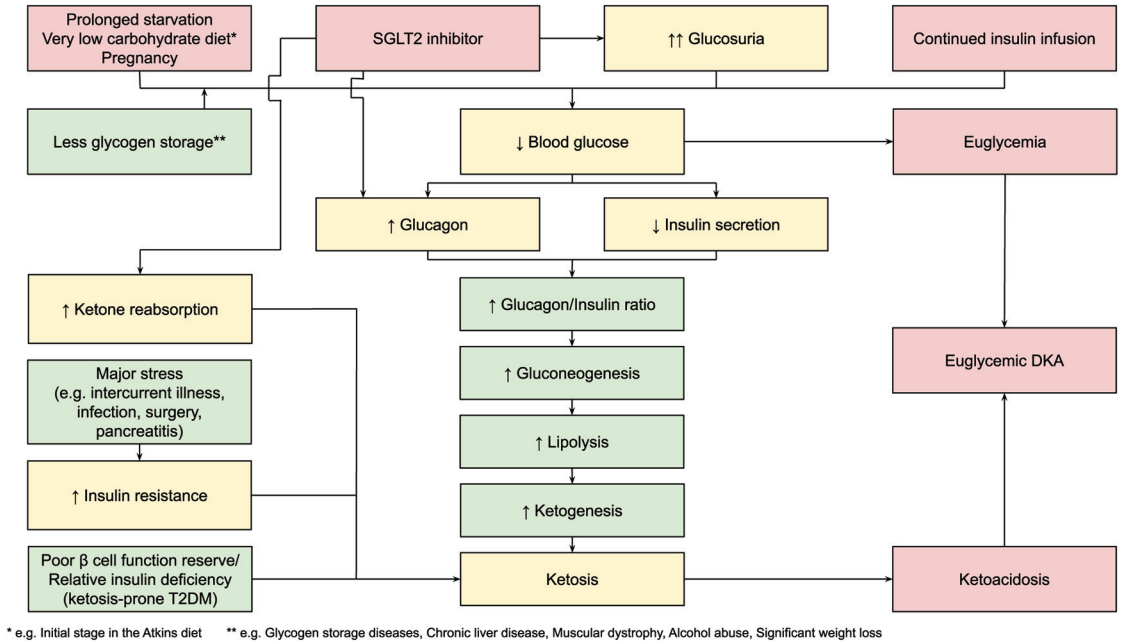

Figure 1. Overall pathogenesis of euglycemic diabetic ketoacidosis.

seen in DKA, which are hyperglycemia, ketosis, and metabolic acidosis[13]:

1. A serum glucose of more than 200 mg per dL (more than 11 mmol per L) or a known diagnosis with diabetes mellitus
2. Ketonemia of 3 mmol per L or more, or significant ketonuria defined as more than 2+ on urine dipstick test
3. Acidosis defined by a venous bicarbonate of less than 15 mmol per L or a venous pH of less than 7.3

However, in euglycemic DKA, serum glucose levels are often normal or slightly elevated defined as a serum glucose of less than 200 mg per dL[6]. This poses a challenge in making a diagonosis because other causes of acidosis must also be ruled out first thus, making euglycemic DKA a diagnosis of exclusion.

Differential diagnosis

It is important in the clinic to always note that patients with diabetes mellitus can also develop acidosis from other conditions seen in patients without diabetes. This includes starvation ketosis, alcoholic ketoacidosis, salicylate and tricyclic antidepressant (TCA) poisoning, lactic acidosis, sepsis, pancreatitis, and renal tubular acidosis[31]. Thus, a complete history taking and full physical and mental examination should be taken in these individuals. Starvation ketoacidosis can usually be differentiated from euglycemic DKA by clinical history and physical examination, which would usually reveal the presence of an intercurrent illness as the precipitating factor and starvation occuring as a result of the illness[31,34], as well as a measurement of serum bicarbonate that is usually more than 18 mEq per L[34]. The mechanism of starvation ketoacidosis occurs in individuals with prolonged starvation. A shortage of glucose supply is a result and stimulates the body to produce more glucose via gluconeogenic pathway and eventually results in ketosis[35]. Alcoholic ketoacidosis (AKA) must also be included as a differential diagnosis. AKA typically occurs in patients with chronic alcoholism when alcohol cannot be consumed due to gastrointestinal symptoms such as nausea, vomiting, and abdominal pain. These presenting symptoms are usually the main reasons that make these individuals seek medical attention in the first place. In addition, the diagnosis can be made by verifying a wide anion gap metabolic acidosis and excessive ketone levels. However, unlike in euglycemic DKA, there is a significant bias towards the rise of beta-hydroxybutyrate. This is because in AKA, there is a raised NADH over NAD ratio favoring the change of acetoacetate to beta-hydroxybutyrate[36]. Beta-hydroxybutyrate however, is undetectable on urine test strips that use the nitroprusside reaction frequently seen in clinical practice[36], thus even if urinary ketones turn out to

Table 1. Major differences between diabetic ketoacidosis, euglycemic diabetic ketoacidosis, starvation ketoacidosis and alcoholic ketoacidosis

Features	Diabetic ketoacidosis (DKA)	Euglycemic DKA	Starvation ketoacidosis	Alcoholic ketoacidosis (AKA)
Pathophysiology	Imbalance of insulin and counter-regulatory hormones in diabetics	Imbalance of insulin and counter-regulatory hormones combining with carbohydrate deficit in diabetics	Carbohydrate deficit and increase gluconeogenesis	Increase ketogenesis and relative hypoglycemia
Precipitating factors	Intercurrent illness, insulin deficiency	Intercurrent illness, SGLT-2i, pregnancy, glycogen storage diseases, diet restriction	Prolonged fasting	Chronic alcoholism
Plasma glucose	High	Normal-mild elevated (<200 mg/dL)	Low-normal	Low-normal
Degree of acidosis	Variable (mild-severe)	Variable (mild-severe)	Mild	Variable (mild-severe)
Serum HCO_3	Usually <15 mEq/L	Usually <15 mEq/L	Usually >18 mEq/L	Usually <15 mEq/L

SGLT-2i=sodium-glucose cotransporter-2 inhibitors

be negative, AKA still cannot be ruled out. It is also mindful to always be aware of these differentials may be the precipitating factors of DKA (Table 1).

Management

Euglycemic DKA is diagnosed by exclusion, which may lead to delay in diagnosis as well as delay in treatment. Other causes of wide gap metabolic acidosis must be excluded such as starvation or AKA, lactic acidosis as seen in sepsis, drug intoxications such as aspirin or TCA poisoning, and renal tubular acidosis as described above. Precipitating factors that trigger an episode of euglycemic DKA should always be kept in mind of clinicians treating this life-threatening condition to minimize the time required to make a diagnosis. Therefore, patients diagnosed with euglycemic DKA still require immediate referral for clinical assessment and treatment.

The key concepts in treating euglycemic DKA do not stray afar from typical DKA. Hydration can be achieved by administering an intravenous infusion of 0.9% sodium chloride at a volume of 1,000 mL during the first hour or extended to 1,500 mL within the first hour according to the American Diabetes Association (ADA) recommendation. After the first hour, the rate of intravenous fluids should be adjusted individually based on the hemodynamic and electrolytes status of each patient. Intravenous solutions can be changed to 0.45% sodium chloride if the sodium concentration of the patient is normal or elevated. Since patients with DKA and euglycemic DKA all have a total body deficit of potassium, potassium replacement is indicated. Replacements can be done by adding 20 to 30 mmol per L (20 to 30 mEq per L) of potassium to each litre of intravenous fluid when serum potassium levels are less than 5.2 mmol per L (less than 5.2 mEq per L) according to the ADA, or can be done by adding 40 mmol per L (40 mEq per L) in each litre of intravenous fluid when potassium concentrations are less than 5 mmol per L (5 mEq per L) according to the Joint British Diabetes Society. Intravenous regular insulin is started after administration of initial fluids at an initial dose of 0.1 units per kg bolus followed by a 0.1 units per kg per hour or a bolus may not be given at all according to the ADA and the Joint British Diabetes Society, respectively. However, lower dose of initial insulin infusion or early administration of dextrose solution is considered due to the milder degree of hyperglycemia, which is charateristic of euglycemic DKA. Individual adjustment of dextrose infusion and insulin infusion rate is essential until DKA has resolved. Another method to adjust insulin can be done according to hourly direct measurement values of beta-hydroxybutyrate. Increasing insulin infusion rates by 1 unit per hour to achieve a reduction in serum ketones at a rate of at least 0.5 mmol per L per hour (5.2 mg per dL per hour) can be done, or in the setting, if the measurement of serum beta-hydroxybutyrate is unavailable, increasing insulin infusion rates by 1 unit per hour to achive an increase of serum bicarbonate at a rate of 3 mmol per L per hour or more (3 mEq per L per hour or more) or a decrease in serum glucose at a rate of 3 mmol per L per hour or more (more than 50 mg per dL per hour) is also acceptable. Insulin causes hypokalemia by promoting the shift of potassium into the intracellular compartment, thus it is not recommended to start administration of insulin if potassium concentrations are less than 3

mmol per L[37]. As for bicarbonate replacement, it is rarely indicated for a condition such as DKA. Studies in the past have also shown that administration of bicarbonate does not offer any advantage in improving the outcomes or rate of recovery from hyperglycemia or ketoacidosis[38]. It otherwise, has potential to increase the risk of developing hypokalemia and cerebral edema[34]. Treating the underlying cause that triggered the episode is also essential for resolution of euglycemic DKA.

Prevention of occurrence is also important in some clinical settings such as pregnancy, especially during the last trimester[31,33,37]. Monitoring of serum ketones is required because euglycemic DKA develops in the absence of hyperglycemia and as such cannot be detected by serum glucose monitoring. Direct laboratory measurement of serum beta-hydroxybutyrate is the preferred option due to its preciseness in a clinical setting but alternative laboratory testing such as blood ketone meter or urine testing is sufficient for patient use in detecting ketosis and early development of euglycemic DKA defined as a serum ketone concentration of more than 0.6 mmol per L or trace (or greater) urine ketones on urine testing. Danne et al[39] has recommend patient self measurement of capillary blood ketones, specifically beta-hydroxybutyrate, as a routine in assessing the metabolic state of patients diagnosed with T1D prescribed with SGLT-2i. For patients who are unable to afford capillary blood ketone measurements, urine testing is also acceptable[39]. It is also important to note that the ketone detected in the urine is acetoacetate and not beta-hydroxybutyrate, and that such estimations will be only an average of the concentration within the urine held in the bladder since the last void. Moreover, because dehydration occurs in patient's with DKA, urine output is decreased and it could take several hours until there is sufficient urine produced, which may lead to a delay for appropriate treatment. Beta-hydroxybutyrate is also oxidised to acetoacetate with treatment of DKA, as such urine ketone measurements will rise even though serum beta-hydroxybutyrates levels drop. This produces a paradoxical rise in urinary ketones and may lead to a false impression that DKA has not yet resolved. Thus, a single ketone measurement is not a reliable source to determine the patient's metabolic state. For patients with elevated ketone levels, glucose and ketone measurements should be checked every 1 to 3 hours to ensure resolution of ketosis and checked repetitively as long as symptoms of DKA persist or stressors remain[1,39].

Currently, there are still no specific testing regimens for euglycemic DKA. For patients who are prescibed with SGLT-2i, signs of nausea, vomiting, or abdominal discomfort should prompt discontinuation of the agent and an evaluation of ketosis. SGLT-2i should be withheld immediately if the patient was hospitalized, acutely ill, or unable to eat and drink normally or withheld at least three days before any major surgical procedures[23,39]. As for patients who are switching to insulin therapy or changing from manual mode to an automated insulin delivery system, it is essential that they hold their SGLT-2i until insulin doses are adjusted, blood glucose is controlled, and ketone levels normalize accordingly[39]. Currently, SGLT-2i is a potential adjunct therapy to insulin for patients with T1D. Some studies have shown a multitude of positive effects including reduced HbA1c and glycemic variability, weight loss, and lower hypoglycemia; however, because of an increase risk for DKA due to a shift toward more ketone production, the European Medicine Agency (EMA) approved this agent for patients with T1D older than 18 years with a body mass index greater than 27 kg per m^2. As such, all patients should receive thorough instructions on DKA risk factors, ketone monitoring, and treatment protocols and only practitioners who have knowledge in the principles of SGLT-2i therapy should prescribe these agents[15,18,20,22,24,39].

Conclusion

Euglycemic DKA is a life-threatening endocrinological emergency characterized differently from its typical counterpart by normalized or slightly elevated plasma levels of glucose defined as less than 200 mg per dL, which can result in delay diagnosis and treatment. This condition can occur in both T1D and T2D. Common causes of euglycemic DKA include prescription and use of SGLT-2i, pregnancy, glycogen storage diseases, diet restriction or starvation, and states of stress such as post-operative states, acute pancreatitis, infections, or intercurrent illnesses. As with DKA, patients with euglycemic DKA also require immediate emergency evaluation and treatment. The treatment includes rapid correction of dehydration along with correction of electrolytes and use of continuous intravenous insulin with a dextrose infusion until the blood glucose is controlled, the wide anion gap metabolic acidosis is resolved, and the ketone values normalizes. It is important for these patients to be educated on signs and presenting symptoms that should alert medical attention, risk factors leading to DKA, ketone monitoring, and treatment protocols for a better and effective treatment

and outcome while practitioners must also be aware of the unwanted side-effects of SGLT-2i.

Further studies: suggestions and knowledge gap

As of the present study, it is still unclear what is the actual trigger of euglycemic DKA. The introduction of SGLT-2i have only covered an amount of ground on the epidemiology, etiology, pathogenesis, and outcomes of patients diagnosed with this condition and yet there is still no current specific testing regimen available to increase its detection. The authors would also suggest for further studies to be conducted on the epidemiology and outcomes of patients diagnosed with euglycemic DKA in Thailand for a clearer understanding of the entity.

What is already known on this topic?

DKA is a life-threatening endocrinological emergency characterized by a classical clinical triad consisting of hyperglycemia, ketonemia, and metabolic acidosis. However, a new entity called euglycemic DKA has emerged and is characterized by milder degrees of hyperglycemia. This can be misleading and result in delayed diagnosis and treatment.

What this study adds?

Since the introduction of SGLT-2i, several case reports and case series have described euglycemic DKA occurring in the patients treated with this agent, suggesting that euglycemic DKA might not occur so infrequently. Other causes of euglycemic DKA include pregnancy, glycogen storage diseases, diet restriction or starvation, and states of stress such as post-operative states, acute pancreatitis, infections, or intercurrent illnesses. It is important for these patients to be educated on signs and presenting symptoms that should alert medical attention, risk factors leading to DKA, ketone monitoring, and treatment protocols for a better and effective treatment and outcome.

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Conflicts of interest

The authors declare no conflict of interest.

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