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Euglycemic diabetic ketoacidosis

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A B S T R A C T

Euglycemic DKA (eu-DKA) is a life-threatening emergency. It may occur in patients with both type 1 and type 2 DM, and characterized by milder degrees of hyperglycemia with blood glucose level < 200 mg/dl, which can result in delayed diagnosis and treatment with potential for adverse metabolic consequences.

Following the wide introduction of the sodium glucose transporter 2 inhibitors (SGLT2i) in therapeutic practice for DM type 2 treatment the amount of eu-DKA increased and therefore, interest to this entity rose. Other causes associated with eu-DKA include pregnancy, decreased caloric intake, heavy alcohol use, insulin use prior to hospital admission, cocaine abuse, pancreatitis, sepsis, chronic liver disease and liver cirrhosis.

Patients with eu-DKA as well as with DKA need immediate referral for emergency evaluation and treatment.

The treatment includes rapid correction of dehydration, correction electrolyte abnormalities, and use of insulin drip until the anion gap, and bicarbonate levels normalize. Increased glucose administration using higher percentages of dextrose (10 or 20%) are required to facilitate the concomitant administration of the relatively large amounts of insulin that are needed to correct the severe acidosis in these patients.

1. Introduction

Diabetic Ketoacidosis (DKA) is a serious and well-studied complication of diabetes mellitus (DM). DKA is a life-threatening emergency and it may occur in patients with both type 1 and type 2 DM.

DKA is defined by the triad of hyperglycemia, anion gap metabolic acidosis and ketonemia. In the most accepted classifications of DKA: the Joint British Diabetes Societies guideline for the management of diabetic ketoacidosis and the diagnostic criteria proposed by the American Diabetes Association (ADA) the level of blood glucose for diagnosis of DKA is over 200 mg/dl (11 mmol/l) [1] or over 250 mg/dl (13.9 mmol/l) respectively [2,3].

In 1973 Munro et al. described a new entity called euglycemic DKA. In a series of 211 episodes of diabetic metabolic decompensation, 37 had severe euglycemic ketoacidosis (a blood sugar level of < 300 mg/100 ml and plasma bicarbonate of 10 mEq/l or less). All were young insulin-dependent diabetics, only one being previously undiagnosed [4].

Euglycemic diabetic ketoacidosis (eu-DKA) is characterized by milder degrees of hyperglycemia with blood glucose values, often < 200 mg/dl, which can result in delayed diagnosis and treatment with potential for adverse metabolic consequences [5].

Following the introduction of the sodium glucose transporter 2 inhibitors (SGLT2i) in therapeutic practice for type 2 DM treatment, there have been several case reports and case series published describing eu-DKA patients treated with these agents [6,7]. Other causes associated with eu-DKA include pregnancy, decreased caloric intake, heavy alcohol use, insulin use prior to hospital admission, cocaine abuse, pancreatitis, sepsis, chronic liver disease and liver cirrhosis [8,9]. An awareness of these factors is important so as to avoid missing a diagnosis of DKA and delaying therapy.

A point worth emphasizing is that eu-DKA might easily be missed based on only clinical signs, given that it is not necessarily associated with typical manifestations of DKA such as dehydration induced by marked hyperglycemia. For example, the patients with eu-DKA treated with a SGLT2i may have less polyuria and polydipsia due to the milder degree of hyperglycemia, and may instead present with malaise, anorexia, tachycardia, or tachypnea with or without fever [6,10]. Severe metabolic acidosis alone has the potential to become a life-threatening condition, however [11].

Patients with eu-DKA as with DKA need immediate referral for emergency evaluation and treatment.

Abbreviations: DM, diabetes mellitus; DKA, diabetic ketoacidosis; Eu-DKA, euglycemic DKA; Nicotin, amideadenine dinucleotide (NAD); SGLT2i, sodium glucose transporter 2 inhibitors; CPT-I, palmitoyl-transferase–I; AKA, alcoholic ketoacidosis; LADA, Latent autoimmune diabetes of adult

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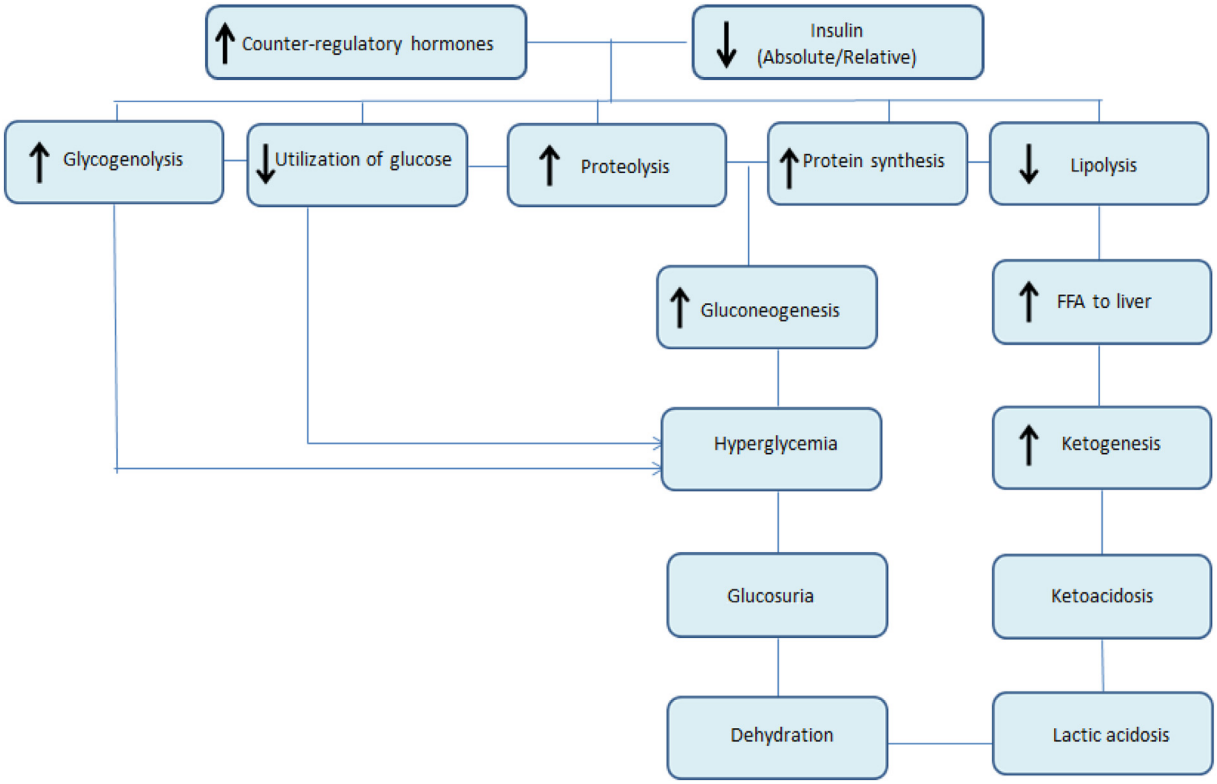

Fig. 1. Pathogenesis of DKA.

2. Pathogenesis of Eu-DKA

Glycemic control is achieved when there is a balance between the insulin levels and the levels of counter-regulatory hormones like glucagon, growth hormone, glucocorticoids and cathecolamines, all of which oppose the action of any residual circulating insulin. This hormonal milieu promotes increased hepatic glucose production, decreased peripheral insulin sensitivity and hyperglycemia.

DKA occurs when there is absolute or relative insulin deficiency in association with increased circulating levels of counter-regulatory hormones, which causes hyperglycemia. The pathogenesis of DKA is shown in Fig. 1.

When a diabetic patient is exposed to any triggering factor for DKA and is fasting or starving while continuing with insulin treatment, the liver will be in a state of glycogen depletion, thereby producing a lesser amount of glucose. On the other hand, there will be lipolysis and fatty acid production, which finally leads to excessive ketone body production [12].

Ketosis results from restriction of carbohydrate usage with increased reliance on fat oxidation for energy production. Absolute insulin deficiency correlates with enhanced lipolysis, which leads to the breakdown of triglycerides into glycerol and high circulating levels of free fatty acids.

Increased delivery of free fatty acids to the liver coupled with raised glucagon levels promotes free fatty acids oxidation and production of ketone bodies. Increased concentrations of glucagon lower hepatic levels of malonyl coenzyme A (CoA), the first rate-limiting enzyme in de novo fatty acid synthesis. Decreased levels of malonyl-CoA then stimulate the rate-limiting enzyme of ketogenesis (carnitine O-palmitoyltransferase 1, liver isoform (CPT1-L)), which promotes transesterification of fatty acyl carnitine and oxidation of free fatty acids to ketone bodies (acetoacetate and β-hydroxybutyrate). Thus, production of ketone bodies is accelerated as a result of increased fatty acyl CoA and CPT1-L activity [13].

In addition, metabolism and clearance of ketone bodies are decreased in states of DKA. Ketone bodies are strong acids that, when present at high levels, can cause metabolic acidosis [13].

In eu-DKA, insulin deficiency and insulin resistance are milder (and insulin resistance may actually be improved); therefore, glucose overproduction and underutilization are quantitatively lesser than in DKA. More importantly, renal glucose clearance (i.e., the ratio of glucosuria to prevailing glycemia) is twice as large with eu-DKA as with DKA [14].

The underlying mechanism of eu-DKA is either due to decreased hepatic production of glucose during the fasting state or enhanced urinary excretion of glucose induced by an excess of counter-regulatory hormones, the former being the most common reason. The possible causes and pathogenetic mechanisms of eu-DKA are shown in Fig. 2.

3. Common causes of eu-DKA

3.1. Eu-DKA in patients with pregnancy

DKA during pregnancy is a serious complication in both the mother and the fetus. Most incidences occur during late pregnancy in women with type 1 DM and to a lesser extent in women with type 2 DM, gestational diabetes, and even newly diagnosed type 1 DM. Approximately 1–3% of pregnant women with impaired glucose tolerance experience DKA [15,16].

With improved clinical care, the incidence of pregnancy related DKA has gradually decreased. However, it remains an important problem because it tends to occur at blood glucose levels that are lower than those in non-pregnant diabetic women [17]. DKA occurs at lower glucose levels because pregnancy is a ketosis-prone state [17,18].

In pregnancy, there is a relative state of accelerated starvation, especially in the second and third trimesters. The fetus and the placenta use large amounts of maternal glucose as a major source of energy, and this leads to decreased maternal fasting glucose. This associated with relative insulin deficiency leads to an increase production of free fatty acids, which are then converted to ketones in the liver [8].

Several physiologic mechanisms influence on the carbohydrates

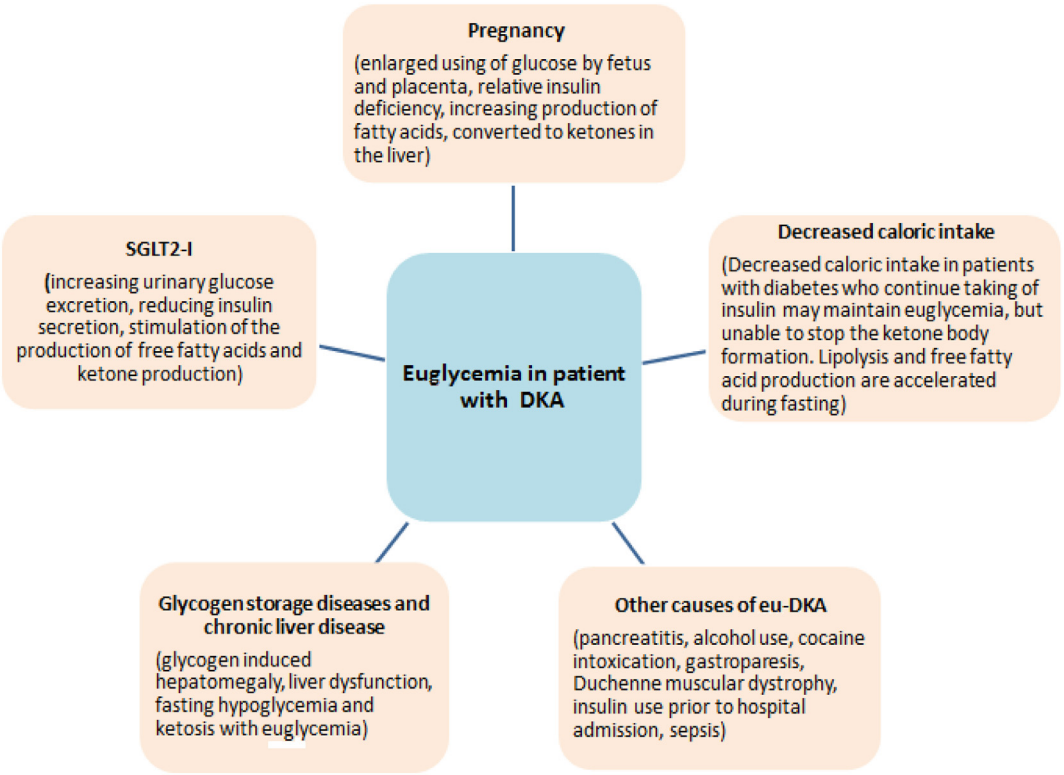

Fig. 2. Possible etio-pathogenetic mechanisms of euglycemic DKA.

balance in pregnancy. On one hand, exists mechanisms that induced insulin resistance and hyperglycemia in pregnancy: the activity of usual counter regulatory hormones (progesterone, estrogen, human placental lactogen and secretion of TNF-α) [19].

During late pregnancy the fetus dramatically increases its glucose-based metabolism and accentuates its anabolic process by growth. On the other hand, the maternal metabolism enters a catabolic process in order to send all the glucose to the fetus through the placenta, using fat as the primary fuel. In the diabetic patient, the decrease in insulin intake profoundly affects the general metabolism, particularly at the level of liver, muscle, and adipose tissue, which are insulin essential action points. The absence of this hormone causes distortion of homeostasis. Plasma levels of glucose, free fatty acids and ketones rise to extreme figures, plasma pH and bicarbonate fall dangerously and there is marked loss of fatty tissue and body mass. If insulin levels are not restored, this case can lead to death [9].

Finally, the respiratory alkalosis that occurs during pregnancy increases the urinary excretion of bicarbonate, reducing the ability to buffer pH changes caused by the increase in body ketone production [15]. This leads to euglycemic diabetic ketoacidosis in pregnancy.

In one study, for example, plasma glucose levels of < 200 mg/dL were present in 4 of the 11 pregnant diabetic patients (36%), 10 (90%) of whom presented with nausea, vomiting, and decreased caloric intake. Despite modern methods of diabetes care, near-normal plasma glucose levels are not enough to preclude diabetic ketoacidosis. Nausea, vomiting, and decreased caloric intake in an otherwise normal pregnant diabetic woman require evaluation to exclude ketosis [18].

Therefore, it is very important to make a prompt diagnosis and start treatment as early as possible in these patients.

3.2. Eu-DKA induced by SGLT2 inhibitors

Sodium-glucose cotransporter 2 inhibitors (SGLT2i) are newly launched oral hypoglycemic drugs indicated for type 2 DM that prevent the reabsorption of glucose from primary urine at the proximal renal tubules by targeting SGLT2 [11].

Their favorable clinical profile has led to increased interest in SGLT2i by health care providers and wide use of these agents in clinical practice.

Recent evidence suggests that eu-DKA might occur not so infrequently in individuals treated with SGLT2i [6,7,20,21]. In patients with type 2 DM, the estimated incidence rates of DKA were 0.52 and 0.76 per 1000 patient-years for 100 and 300 mg of canagliflozin, respectively [22,23]. The rate of reported DKA was < 0.1% in empagliflozin-treated patients with type 2 DM [24].

SGLT2i lower blood glucose levels by increasing urinary glucose excretion, which in turn reduces insulin secretion from pancreatic β-cells. The decline in circulating insulin levels results in a lowering of the anti-lipolytic activity of insulin and consequent stimulation of the production of free fatty acids, which are converted to ketone bodies by β-oxidation in the liver. Moreover, insulin stimulates the activity of acetyl-CoA carboxylase, which produces malonyl-CoA, a potent inhibitor of carnitine palmitoyl-transferase–I (CPT−I). Given that CPT-I promotes the transport of insulin in individuals with impaired insulin secretion, caution is warranted in dispensing these drugs for such patients [11].

SGLT2i have been associated not only with increases in ketone-associated adverse events [20,25–27]. Recent evidence demonstrating the presence of SGLT2 in pancreatic α-cells has not only shed light on why and how SGLT2i therapy directly stimulated glucagon secretion from α-cells, but also uncovered how SGLT2i may exaggerate ketogenesis, gluconeogenesis, and glycogenolysis via further reduction of the insulin-to-glucagon ratio. In contrast to glucosuria, which leads to declining blood glucose levels, gluconeogenesis and glycogenolysis elevate glucose levels. Accordingly, the hyperglycemic or euglycemic presentation of DKA in type 2 DM depends on the equilibrium achieved between endogenous glucose production and renal glucose clearance [20,28–30].

Risk factors for eu-DKA with SGLT2i include latent autoimmune diabetes of adulthood (LADA), surgery, low carbohydrate diets, insulin

withdrawal or dose reduction, and acute medical illness [20,21,24,31].

In one review authors analyzed 46 case reports of patients with SGLT2i–associated DKA [20]. Twenty-four of these individuals had type 2 DM, 2 patients had pancreatic (type 3c) diabetes, 15 had type 1 DM, and 5 had latent autoimmune diabetes in adulthood (LADA) [20]. Interestingly that thirty-two (70%) of the 46 patients had euglycemic DKA, thirteen of the 24 patients with type 2 diabetes were taking insulin and/or a sulfonylurea [20]. Common precipitants of DKA in these case reports were inappropriate insulin reduction or omission among those who were insulin-deficient, bariatric or other surgery, excessive alcohol intake, physical exertion/exercise, and a dietary restriction (low-carbohydrate or reduced intake) [20]. The authors of this review emphasized, that although the SGLT2i was a likely contributor to DKA, it is possible that at least some of these events could have occurred even in the absence of SGLT2i therapy due to other important etiologic triggers [20].

Therefore, the complete history and clinical evaluation of all patients with eu-DKA is important for a true understanding of all causes and pathogenetic factors contributing this life-threatening state.

3.3. Eu-DKA in patients with decreased caloric intake and after bariatric surgery

A decrease in caloric intake is frequently associated with the development of DKA, usually due to nausea or vomiting caused by a precipitating illness or by worsening ketoacidosis itself. During these times of decreased caloric intake, patients with diabetes who continue taking sufficient amounts of insulin may maintain euglycemia, but are unable to stop the ketone body formation and can present with DKA with only mild elevations of blood glucose or even relative normoglycemia [4,32–34].

In cases of prolonged fasting, near total glycogen depletion contributes to the normoglycemia as metabolic acidosis continues to develop [35,36].

In addition, lipolysis and free fatty acid production are accelerated during fasting [37], and insulin is less effective at suppressing lipolysis and ketogenesis during this state [38], exacerbating the development of acidosis.

In one study the authors describe two patients with type 1 DM, one from them had a history of failed insulin pump two days before admission and decreased food intake, the second patient, had urinary tract infection in conjunction with nausea due to the infection, causing a decreased calorie intake and led to ketoacidosis with euglycemia [13].

In the other case the authors describe cases of eu-DKA precipitated by starvation resulting from severe depression in a patient with type 1 DM [32].

Bariatric surgery for obesity is increasing in patients with DM. The incidence of DKA is up to 1 in 4 of patients with type 1 DM following bariatric surgery [39,40]. Patients undergoing bariatric surgery may be especially at risk of DKA, as they experience both surgery and extended fasting peri-operatively.

One case study described a 43-year-old woman with type 1 DM whose post-operative period following her bariatric surgery was complicated by eu-DKA [41]. The authors concluded that eu-DKA is an important diagnostic consideration due to the potential of missed diagnosis in these patients, as it does not present like a typical DKA episode.

In another case report, the authors describe a patient who appropriately stopped her SGLT2i, canagliflozin 24 h before surgery and subsequently developed life-threatening eu-DKA [42].

3.4. Eu-DKA in patients with glycogen storage diseases and chronic liver disease

Glycogen storage disorders as well as chronic liver disease resulting in decreased glycogen stores can also result in euglycemic ketoacidosis [32,43].

Glycogen storage disease type VI (Hers disease) is caused by the deficiency of liver glycogen phosphorylase, suspected as an autosomal recessive inheritance and had the mutations of *PYGL* gene [44,45]. Patients with type 1 DM and glycogen storage disease type VI have some similar clinical features such as glycogen induced hepatomegaly, liver dysfunction, fasting hypoglycemia and ketosis with euglycemia [43]. The differences between them are the age-at-onset of disease; i.e. youth period versus infantile period, and the background of disease; i.e. the state of type 1 diabetes versus the hereditary enzyme deficiency.

3.5. Other causes of eu-DKA

Some of the not very common causes of eu-DKA that have been reported in the literature are acute pancreatitis [46,47], eu-DKA in patients due to heavy alcohol use [32], cocaine intoxication [48], eu-DKA due to gastroparesis [49], eu-DKA in a patients with type 1 and type 2 DM and Duchenne muscular dystrophy [50,51].

4. Differential diagnosis

In clinical practice it must be remembered that patients with DM may be at risk of developing acidosis from conditions that are also seen in patients without DM, and a distinction between non-diabetic eu-DKA and eu-DKA is essential. The former includes differential diagnoses, such as prolonged starvation, excess alcohol consumption, salicylate overdose, lactic acidosis, tricyclic antidepressant overdose, and renal tubular acidosis, while the latter is a complex pathophysiological process specific to individuals with severe insulin deficiency [3,4,32].

Starvation ketoacidosis can be differentiated from eu-DKA by clinical assessment (one would usually expect the presence of an intercurrent illness to act as a precipitant for eu-DKA, with the starvation possibly occurring as a result of the intercurrent illness rather than as a primary event) and measurement of the serum bicarbonate concentration, which in starvation ketosis is usually not lower than 18 mEq/l [3,32].

In practice there may be a considerable degree of overlap between starvation ketoacidosis and eu-DKA, as the relative normoglycemia in eu-DKA occurs as a result of prolonged fasting [32,52,53].

Alcoholic ketoacidosis (AKA) typically develops in patients who depend on alcohol for their small supply of carbohydrates due to chronic alcoholism, and occurs when alcohol can no longer be consumed due to symptoms such as nausea, vomiting, or abdominal pain. These gastrointestinal symptoms are the main reasons for medical attention. In addition to this typical medical history and clinical features, diagnoses are made by verifying metabolic acidosis with an increased anion gap and excessive ketone body production. However, unlike DKA, AKA is characterized by the significant bias towards β-hydroxybutyrate of produced ketone bodies compared with acetoacetate, due to the rising NADH/NAD ratio. β-Hydroxybutyrate cannot be detected with urine test strips that use the nitroprusside reaction frequently used in routine medical care, and even if urinary ketone is negative, AKA cannot be ruled out [54].

5. Recommendations for management of patients with eu-DKA

Because that eu-DKA present with normal or moderately increased blood glucose level, it may lead to delays in recognition or diagnosis and delayed treatment of this life-threatening medical condition. Patients presenting with eu-DKA as well as patients with DKA need immediate referral for emergency evaluation and treatment.

Diagnosis of eu-DKA is difficult as it is primarily a diagnosis of exclusion. Other forms of ketoacidosis like starvation ketoacidosis has to be ruled out. Also, other causes of increased anion gap metabolic acidosis like lactic acidosis, increased toxic serum alcohols (methanol, ethylene glycol, etc.), drug toxicity, paraldehyde ingestion and renal

failure have to be excluded [13,48]. Clinicians should be aware of the possible etiological triggers of eu-DKA in susceptible patients and actively rule out other differentials thereby minimizing the time required for diagnosing eu-DKA [13]. If diagnosed early and managed aggressively with fluids and insulin drip, eu-DKA may be easily reversed, thus minimizing morbidity and mortality [9,13]. The correct diagnosis of eu-DKA is also necessary to tailor therapy accordingly.

Once diagnosed, management of eu-DKA is simple and is similar to the management of DKA [3,4,13,32]. The mainstay of treatment involves rapid correction of dehydration using intravenous fluids and correction electrolyte abnormalities [3,4,13,35,55]. The second most important step in the management is the use of an insulin drip along with a dextrose containing solution until the anion gap, and bicarbonate levels normalize [24].

Increased glucose administration using higher percentages of dextrose (10 or 20%) are required to facilitate the concomitant administration of the relatively large amounts of insulin that are needed to correct the severe acidosis in these patients [3,4,32,56,57].

It is very important in several cases to prevent occurrence of eu-DKA in relevant situations.

For example, careful management of DM in pregnant women particularly in the last trimester of pregnancy is very important to prevent decompensation and the occurrence DKA including eu-DKA.

The most effective means of preventing SGLT2i–associated DKA is to ensure that SGLT2i are appropriately prescribed and are withheld during any situation that might precipitate DKA (e.g., acute illness, surgery, dehydration, excessive alcohol intake). Given that the half-life of the SGLT2i ranges from 11 to 13 h, and the SGLT2i effect can persist for at least a few days after discontinuation, these agents should be discontinued approximately 3 days before major surgical procedures or during periods of acute illness [20]. Providers treating patients with type 1 DM off-label should withhold the drug if patients experience any symptomatic ketonuria or ketonemia [6,22]. All patients with type 2 DM should be educated regarding sufficient hydration and adequate carbohydrate intake while using SGLT2i. Clinicians should avoid using SGLT2i in patients who are unable to tolerate oral food intake, perioperatively, with extreme weight loss, and on very low carbohydrate diet [22,58].

6. Conclusion

Eu-DKA is a life-threatening emergency and characterized by milder degrees of hyperglycemia with blood glucose level < 200 mg/dl, which can result in delayed diagnosis and treatment with potential for adverse metabolic consequences.

Following the wide introduction of the sodium glucose transporter 2 inhibitors (SGLT2i) in therapeutic practice for type 2 DM treatment, the amount of eu-DKA increased.

Patients with eu-DKA as well as with DKA need immediate referral for emergency evaluation and treatment. The treatment includes rapid correction of dehydration, correction electrolyte abnormalities, and use of insulin drip until the anion gap and bicarbonate levels normalize. Increased glucose administration using higher percentages of dextrose (10 or 20%) are required to facilitate the concomitant administration of the relatively large amounts of insulin that are needed to correct the severe acidosis in these patients.

References

[1] Savage MW, Dhatariya KK, Kilvert A, et al. Joint British Diabetes Societies guideline for the management of diabetic ketoacidosis. Diabet. Med. 2011;28(5):508–15.
[2] American Diabetes Association. Diabetes Care. 29. 2006.
[3] Kitabchi AE, Umpierrez GE, Miles JM, Fisher JN. Hyperglycemic crises in adult patients with diabetes. Diabetes Care 2009;32:1335–43.
[4] Munro JF, Campbell IW, McCuish AC, Duncan LJ. Euglycaemic diabetic ketoacidosis. Br Med J 1973;2(5866):578–80.
[5] Modi A, Agrawal A, Morgan F. Euglycemic diabetic ketoacidosis: a review. Curr Diabetes Rev 2017;13(3):315–21.
[6] Peters AL, Buschur EO, Buse JB, Cohan P, Diner JC, Hirsch IB. Euglycemic diabetic ketoacidosis: a potential complication of treatment with sodium-glucose cotransporter 2 inhibition. Diabet Care 2015;38(9):1687–93.
[7] Meyer EJ, Gabb G, Jesudason D. SGLT2 inhibitor-associated euglycemic diabetic ketoacidosis: a south Australian clinical case series and Australian spontaneous adverse event notifications. Diabetes Care 2018;41(4):e47–9.
[8] Kamalakannan D, Baskar V, Barton DM, Abdu TAM. Diabetic ketoacidosis in pregnancy. Postgrad Med J 2003;79:454–7.
[9] Lucero P, Chapela S. Euglycemic diabetic ketoacidosis in the ICU: 3 case reports and review of literature. Case Rep Crit Care 2018:1747850https://doi.org/10.1155/2018/1747850.
[10] Ahmed M, McKenna MJ, Crowley RK. Diabetic ketoacidosis in patients with type 2 diabetes recently commenced on SGLT-2 inhibitors: an ongoing concern. Endocr Pract 2017;23(4):506–8.
[11] Ogawa W, Sakaguchi K. Euglycemic diabetic ketoacidosis induced by SGLT2 inhibitors: possible mechanism and contributing factors. J Diabetes investing 2016;7(2):135–8.
[12] Kitabchi AE, Umpierrez GE, Miles JM, Fisher JN. Hyperglycemic crises in adult patients with diabetes. Diabetes Care 2009;32:1335–43. https://doi.org/10.2337/dc09-9032.
[13] Umpierrez G, Korytkowski M. Diabetic emergencies — ketoacidosis, hyperglycaemic hyperosmolar state and hypoglycaemia. Nat Rev Endocrinol 2016;12(4):222–32.
[14] Rosenstock J, Ferrannini E. Euglycemic diabetic ketoacidosis: a predictable, detectable, and preventable safety concern with SGLT2 inhibitors. Diabetes Care 2015;38(9):1638–42.
[15] Parker JA, Conway DL. Diabetic ketoacidosis in pregnancy. Obstet Gynecol Clin North Am 2007;34:533–43. https://doi.org/10.1016/j.ogc.2007.08.001.
[16] Reece EA, Coustan DR, Gabbe SG. Diabetes in women: Adolescence, pregnancy, and menopause. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2004.
[17] Guo RX, Yang LZ, Li LX, Zhao XP. Diabetic ketoacidosis in pregnancy tends to occur at lower blood glucose levels: case–control study and a case report of euglycemic diabetic ketoacidosis in pregnancy. J Obstetr Gynaecol Res 2008;34:324–30. https://doi.org/10.1111/j.1447.0756.2008.00720.x.
[18] Cullen MT, Reece EA, Homko CJ, Sivan E. The changing presentations of diabetic ketoacidosis during pregnancy. Am J Perinatol 1996;13:449–51.
[19] Dalfr'a MG, Burlina S, Sartore G, Lapolla A. Ketoacidosis in diabetic pregnancy. J Matern Fetal Neonatal Med 2016;29(17):2889–95. https://doi.org/10.3109/14767058.2015.1107903.
[20] Goldenberg RM, Berard LD, Cheng AY, et al. SGLT2 inhibitor-associated diabetic ketoacidosis: clinical review and recommendations for prevention and diagnosis. Clin Ther 2016;38(12):2654–64. [e1].
[21] Hine J, Paterson H, Abrol E, et al. SGLT inhibition and euglycaemic diabetic ketoacidosis. Lancet Diabetes Endocrinol 2015;3:503–4.
[22] Oiu H, Novikov A, Vallon V. Ketosis and diabetic ketoacidosis in response to SGLT2 inhibitors: basic mechanisms and therapeutic perspectives. Diabetes Metab Res Rev 2017;33:e2886https://doi.org/10.1002/dmrr.2886.
[23] Erondu N, Desai M, Ways K, Meininger G. Diabetic ketoacidosis and related events in the Canagliflozin type 2 diabetes clinical program. Diabetes Care 2015;38:1680–6.
[24] Rosenstock J, Ferrannini E. Euglycemic Diabetic Ketoacidosis: a predictable, detectable, and preventable safety concern with SGLT2 inhibitors. Diabetes Care 2015;38(9):1638–42.
[25] Pieber TR, Famulla S, Eilbracht J, et al. Empagliflozin as adjunct to insulin in patients with type 1diabetes: a4-week, randomized, placebo-controlled trial (EASE-1). Diabetes Obes Metab 2015;17:928–35.
[26] Inagaki N, Kondo K, Yoshinari T, et al. Efficacy and safety of canagli- flozin in Japanese patients with type 2 diabetes: a randomized, double- blind, placebo-controlled, 12-week study. Diabetes Obes Metab 2013;15:1136–45.
[27] Kaku K, Watada H, Iwamoto Y, et al. Efficacy and safety of monotherapy with the novel sodium/glucose cotransporter-2 inhibitor to fogliflozin in Japanese patients with type 2 diabetes mellitus: a combined Phase 2 and 3 randomized, placebo-controlled, double-blind, parallel-group comparative study. Cardiovasc Diabetol 2014;13:65.
[28] Bonner C, Kerr-Conte J, Gmyr V, et al. Inhibition of the glucose transporter SGLT 2 with dapagliflozin in pancreatic alpha cells triggers glucagon secretion. Nat Med 2015;21:512–7.
[29] Ferrannini E, Muscelli E, Frascerra S, et al. Metabolic response to sodium-glucose cotransporter 2 inhibition in type 2 diabetic patients. J Clin Invest 2014;124:499–508.
[30] Merovci A, Solis-Herrera C, Daniele G, et al. Dapagliflozin improves muscle insulin sensitivity but enhances endogenous glucose production. J Clin Invest 2014;124:509–14.
[31] Hayami T, Kato Y, Kamiya H, et al. Case of ketoacidosis by a sodium-glucose cotransporter 2 inhibitor in a diabetic patient with a low-carbohydrate diet. J Diabetes Investig 2015;6:587–90.
[32] Joseph F, Anderson L, Goenka N, Vora J. Starvation-induced true diabetic euglycemic ketoacidosis in severe depression. J Gen Intern Med 2009 Jan;24(1):129–31. https://doi.org/10.1007/s11606-008-0829-0.
[33] Burge MR, Garcia N, Qualls CR, Schade DS. Differential effects of fasting and dehydration in the pathogenesis of diabetic ketoacidosis. Metabolism. 2001;50:171–7.
[34] Foster DW, McGarry JD. The metabolic derangements and treatment of diabetic ketoacidosis. N Engl J Med 1983;309:159–69.
[35] Burge MR, Hardy KJ, Schade DS. Short-term fasting is a mechanism for the development of euglycemic ketoacidosis during periods of insulin deficiency. J Clin

Endocrinol Metab 1993;76:1192–8.
[36] Rothman DL, Magnusson I, Katz LD, Shulman RG, Shulman GI. Quantitation of hepatic glycogenolysis and gluconeogenesis in fasting humans with 13C NMR. Science 1991;254:573–6.
[37] Wolfe RR, Peters EJ, Klein S, Holland OB, Rosenblatt J, Gary HJr. Effect of short-term fasting on lipolytic responsiveness in normal and obese human subjects. Am J Physiol 1987;252:E189–96.
[38] Jensen MD, Haymond MW, Gerich JE, Cryer PE, Miles JM. Lipolysis during fasting. Decreased suppression by insulin and increased stimulation by epinephrine. J Clin Invest 1987;79:207–13.
[39] Kirwan JP, Aminian A, Kashyap SR, et al. Bariatric surgery in obese patients with type 1 diabetes. Diabetes Care 2016;39(6):941–8.
[40] Rottenstreich A, Keidar A, Yuval JB, et al. Outcome of bariatric surgery in patients with type 1 diabetes mellitus: our experience and review of the literature. Surg Endosc 2016;30(12):5428–33.
[41] Dowsett J, Humphreys R, Krones R. Normal blood glucose and high blood ketones in a critically unwell patient with T1DM post-bariatric surgery: a case of euglycemic diabetic ketoacidosis. Obes Surg 2019 Jan;29(1):347–9. https://doi.org/10.1007/s11695-018-3548-6.
[42] Lane S, Paskar D, Hamed S, Goffi A. When guidelines fail: euglycemic diabetic ketoacidosis after bariatric surgery in a patient taking a sodium-glucose co-transporter-2 inhibitor: a case report. A A Pract 2018 Jul 15;11(2):46–8. https://doi.org/10.1213/XAA.0000000000000734.
[43] Tomihira M, Kawasaki E, Nakajima H, et al. Intermittent and recurrent hepatomegaly due to glycogen storage in a patient with type 1 diabetes: genetic analysis of the liver glycogen phosphorylase gene (PYGL). Diabetes Res Clin Pract 2004;65:175–82.
[44] Burwinkel B, Bakker HD, Herschkovitz E, Moses SW, Shin YS, Kilimann MW. Mutations in the liver glycogen phosphorylase gene (PYGL) underlying glycogenosis type VI. Am J Hum Genet 1998;62(4):785–91.
[45] Chang S, Rosenberg MJ, Morton H, Francomano CA, Biesecker LG. Identification of a mutation in liver glycogen phosphorylase in glycogen storage disease type VI. Hum Mol Genet 1998;7(5):865–70.
[46] Prater J, Chaiban J. Euglycemic diabetic ketoacidosis with acute pancreatitis in a patient not known to have diabetes. Endocr Pract 2015;1:e88–91. https://doi.org/10.4158/ep14182.cr.
[47] Thawabi M, Studyvin S. Euglycemic diabetic ketoacidosis, a misleading presentation of diabetic ketoacidosis. N Am J Med Sci 2015;7(6):291–4. https://doi.org/10.4103/1947-2714.157490.
[48] Abu-Abed Abdin A, Hamza M, Khan MS, Ahmed A. Euglycemic diabetic ketoacidosis in a patient with cocaine intoxication. Case Rep Crit Care 2016:4275651https://doi.org/10.1155/2016/4275651.
[49] Legaspi R, Narciso P. Euglycemic diabetic ketoacidosis due to gastroparesis, a local experience. J Ark Med Soc 2015;112(5):62–3.
[50] Braithwaite SS, Lange CF, Klamut M. Euglycemic diabetic ketoacidosis in Duchenne's muscular dystrophy. Diabetes Care 1987;10(4):540–1.
[51] Lee SH, Park JH, Hong MK, et al. True euglycemic diabetic ketoacidosis in a person with type 2 diabetes and Duchenne muscular dystrophy. Diabetes Res Clin Pract 2011;92(1):e7–8. https://doi.org/10.1016/j.diabres.2010.12.015. [Epub 2011 Jan 8].
[52] Jenkins D, Close CF, Krentz AJ, Nattrass M, Wright AD. Euglycaemic diabetic ketoacidosis: does it exist? Acta Diabetol 1993;30:251–3.
[53] Davies RG, De P, Child DF, Gemmell L, Rincon C. Euglycaemic diabetic ketoacidosis. Hosp Med 2003;64:557–8.
[54] Suzuki K, Tamai Y, Urade S, et al. Alcoholic ketoacidosis that developed with a hypoglycemic attack after eating a high-fat meal. Acute Med Surg 2014:109–14. https://doi.org/10.1002/ams2.13.
[55] Gelaye A, Haidar A, Kassab C, Kazmi S, Sinha P. Severe ketoacidosis associated with canagliflozin (Invokana): a safety concern. Case Rep Crit Care 2016:1656182https://doi.org/10.1155/2016/1656182.
[56] McNulty SJ, English PJ. Euglycaemic diabetic ketoacidosis. Pract Diabet Int 2002;19:63.
[57] Franke B, Carr D, Hatem MH. A case of euglycaemic diabetic ketoacidosis in pregnancy. Diabet Med 2001;18:858–9.
[58] Kalra S, Gupta Y, Patil S. Sodium-glucose cotransporter-2 inhibition and the insulin: glucagon ratio: unexplored dimensions. Indian J Endocrinol Metab 2015;19:426–9.