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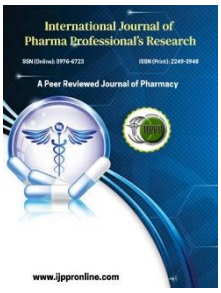

An Overview on Sodium-Glucose Cotransporter 2 (SGLT-2) Inhibitors Induced Euglycemic Diabetic Ketoacidosis: Clinical Manifestation, Mechanism, Diagnosis, Prevention and Treatment

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ABSTRACT: Euglycemic diabetic ketoacidosis is a transient and dangerous metabolic condition characterized by ketoacidosis and considerably lower blood glucose levels which is associated with the usage of newer class of oral antidiabetic medication known as Sodium-glucose cotransporter 2 (SGLT-2) inhibitors. The primary mechanism involved in SGLT2 inhibitors induced eDKA would due to increased lipolysis and ketone body reabsorption. SGLT2i also tend to increase the pancreatic alpha cells, which simultaneously blocks the beta cells, thereby causing an disruption in glucagon/insulin ratio that accounts to enhanced lipolysis and ketogenesis, which is clinically manifested with Fatigueness, stomach pain, nausea and vomiting resulting in reduced blood pressure and dehydration, altered psychological condition, dyspnea, rapid breathing, loss of appetite, pyrexia and tachycardia. Despite lower blood glucose levels or the absence of urine ketones, euglycemic DKA is difficult to diagnose and should be examined in the differential diagnosis of an ill patient who as a previous history of diabetes mellitus. eDKA is often triggered by insulin absence or dose drop, severe acute sickness, dehydration, strenuous activity, surgeries, low-carbohydrate meals, or heavy alcohol or drug abuse. Making the definitive diagnosis using conventional diagnostic tools and clinical standards, as well as coordinating fluid resuscitation, insulin treatment, and electrolyte replacement based on information gained from prompt patient observing and knowledge of resolution criteria, are all components of management and the prevention method includes patient and physician education on risk and precipitating factors and suspending SGLT2 inhibitors therapy may reduce SGLT2 inhibitor-induced eDKA, which are more critical. This review briefly illustrates on the signs & symptoms, mechanism of induction, investigation and diagnosis, prevention and treatment of

1. Introduction:

Sodium-glucose cotransporter 2 (SGLT2) inhibitors are the most recent group of oral diabetic medicines. The utilization of these medications is expected to grow sharply [1] as they have evolved as an important type of blood glucose-lowering drug due to their weight reduction property, cardiovascular protective role and which is primarily owing to their natriuretic action and renal protective qualities.[6,9,12,14,23] SGLT-2 inhibitors reduce plasma glucose levels by increasing renal glucose excretion, which lowers the insulin-to-glucagon ratio and increases lipolysis, encouraging the formation of ketone bodies in the liver [2-5,8-10] and Glycosuria is promptly caused, resulting in a 0.6% to 0.9% decrease in glycosylated haemoglobin A1c (HbA1c).[24] SGLT-2inhibitors has been linked to uncommon cases of a dangerous and potentially fatal condition called euglycemic diabetic ketoacidosis (eDKA), that includes ketoacidosis with just mild to moderate glucose increase. [3] Adverse negative consequences of SGLT2i therapy should also be examined to assure optimal use, in conjunction to a heightened risk of DKA, there have been incidences of Genito-urinary infections, acute renal failure characterised by albuminuria, and increased risk of limb amputation [5], hypovolemia [12], reduced levels of serum uric acid [21] with the utilization of SGLT2 inhibitors therapy. Patients on SGLT2 inhibitors therapy are also associated with the risk for development of Fournier's gangrene, a potentially fatal and highly proceeding necrotizing soft tissue infectious disease of the external genitalia.[15] The majority of SGLT2 inhibitors associated with development of eDKA have involved canagliflozin, ipragliflozin, and empagliflozin, with very few cases of dapagliflozin being the problematic medicine in emergency department patients.[11,12] When we come to know about diabetic ketoacidosis, it is a transient & potentially lethal consequence of diabetes mellitus [2], The American Diabetes Association (ADA) classifies DKA as blood glucose levels greater than 250 mg/dl, arterial pH greater than 7.3, anion gap greater than 12 mEq/L, bicarbonate ion greater than 15 mEq/L, and the appearance of ketones in blood and urine.[3,22] Whereas euglycemic diabetic ketoacidosis (eDKA) is characterised by absolute euglycemia (blood glucose range lower than 250 mg/dL), associated with metabolic acidosis and ketosis [6], which frequently causes delays in identification and treatment. clinically manifested with Fatigueness, stomach pain, nausea and vomiting resulting in hypotension and dehydration, altered psychological condition. [8-10] Several precipitating elements have been recognized that may enhance the incidence of DKA in individuals with SGLT2i therapy, that includes, Surgery and illness both provoked stressful response [9], enhanced growth hormone, glucagon, and cortisol production, insulin deficiency could result in increased lipolysis & boosting the free fatty acid molecule for ketone body synthesis [25], reduced fluid consumption may affect renal function, resulting in lower excretion of glucose and ketones, raising glycaemic and the ketotic state [5], underpinning infection and malignancy [4], pregnancy, drug & alcohol abuse [7] and reduced carbohydrate ingestion can result in increased glucagon release from pancreatic alpha cells and reduced insulin secretion that would elevate the risk of eDKA.[8] In the cohort study conducted by Fateen Ata et al involving 9940 diabetes mellitus subjects using SGLT2 inhibitors therapy, the estimated prevalence of eDKA was 58.1%. Patients on canaglifozin had the highest rate of eDKA of 100%, preceded by empaglifozin 77%, and dapaglifozin 48.3%, respectively.[26] The purpose of this article is to provide an understanding of the etiology, pathophysiology, diagnosis, prevention, and management of euglycemic diabetic

ketoacidosis induced by SGLT-2 inhibitors therapy.

2. Characteristic features of eDKA induced by SGLT-2 inhibitors:

Euglycemic diabetic ketoacidosis (eDKA) is a transient, uncommon but significant metabolic repercussion [3] precipitated in patients on therapy with SGLT-2 inhibitors for chronic diabetes management are frequently manifested with Fatigueness, stomach pain, nausea and vomiting resulting in reduced blood pressure and dehydration, altered psychological condition [8], elevated beta-hydroxybutyrate and plasma acetone levels, elevated urine ketone bodies as well as an elevated anion gap metabolic acidosis [10], however, some patients have a mixture of normal anion gap and an elevated anion gap metabolic acidosis [9], furtherly, dyspnea, rapid breathing, loss of appetite, elevated body temperature and increase in heart rate [22] have also been associated with SGLT-2 inhibitors induced euglycemic diabetic ketoacidosis.

3. Mechanism by which SGLT2 inhibitors induces euglycemic diabetic ketoacidosis:

Sodium-glucose cotransporter 2 inhibitors (SGLT-2i) depict the latest group of oral diabetes medications, which are found to induce unusual and severe adverse drug reaction known as Euglycemic Diabetic ketoacidosis (eDKA), even the US Food and Drug Administration (FDA) has also released an alert notice regarding SGLT2 inhibitors induced diabetic ketoacidosis. [1] The exact mechanism underlying SGLT-2i-induced eDKA is unknown, but some of the theories have been postulated that includes; It is known that the proximal renal convoluted tubules of nephron are the principal target of action for SGLT2-inhibitors medication and they act by preventing glucose reabsorption, enabling glucosuria which results in decreased insulin production from beta-cells of pancreas, and improving glycaemic control by inhibiting SGLT2 receptors. [2] while the reduced insulin levels are coupled with excessive glucagon, cortisol, and adrenaline levels and a drop in systemic insulin levels causes a reduction in insulin's antilipolytic effect and results in the promotion of free fatty acid synthesis. [3] However, in predisposed individuals, eDKA is triggered by osmotic diuresis, glucosuria, hypovolemia, and dehydration. [4] eDKA may be triggered in individuals on SGLT2i therapy which lowers the insulin need due to enhanced glucosuria and enhances the production of glucagon from alpha cells of pancreas. Hence the switch in insulin: glucagon proportion, results in enhanced lipolysis due to the lack of antilipolytic effect of insulin, as well as glucagon's stimulation of lipase, resulting in an elevated free fatty acid substrate for hepatic ketone bodies (acetoacetate, beta-hydroxybutyrate & acetone) synthesis. [8] Glucagon stimulates the hepatic beta-oxidation of free fatty acids into acetyl CoA, which is essential for ketone body metabolism, thus raising the ketone levels. [5] Enhanced fat oxidations after SGLT2i therapy can aggravate secondary bicarbonate ions loss from the body by impairing absorption and oxidation of filtered b-hydroxybutyrate. The tubule's entire oxidation of ketones provides ATP, which is added to the stock produced by fatty acid oxidation. This elevated ATP contributes to the suppression of ammonia generation and also reduces ketone body absorption and oxidation. These modifications result in, elevated urinary excretion of b-hydroxybutyrate paired to sodium or potassium ion, contributing to acidosis via the body's indirect depletion of bicarbonate ions. [9] Additionally, insulin promotes the function of acetyl-CoA carboxylase, which results in the formation of malonyl-CoA, a significant inhibitor of carnitine palmitoyl transferase-I(CPT-I) while the decline in the circulating amount of insulin boosts the formation of ketone bodies by stimulation of CPT-I, which boosts the transfer of fatty acids into mitochondria and thus raises the rate of beta-oxidation, also the glucagon suppresses acetyl-CoA carboxylase and hence increases CPT-I action in the liver, increased

glucagon secretion is most likely to lead to ketone body excess production. [13] Individuals with eDKA frequently have hypovolemia as a result of osmotic diuresis and a decreased glomerular filtration rate (GFR). In this situation, besides the fact that the renal sensitivity to acidosis is dulled, but also the pace of elimination of ketoacids is reduced, resulting in significant ketonemia [3] additional elevated insulin resistance owing to stress, prolonged fasting, or an aggressive drop in insulin, could shift the patient from ketogenic condition to a typical high anion gap ketoacidosis.[14]

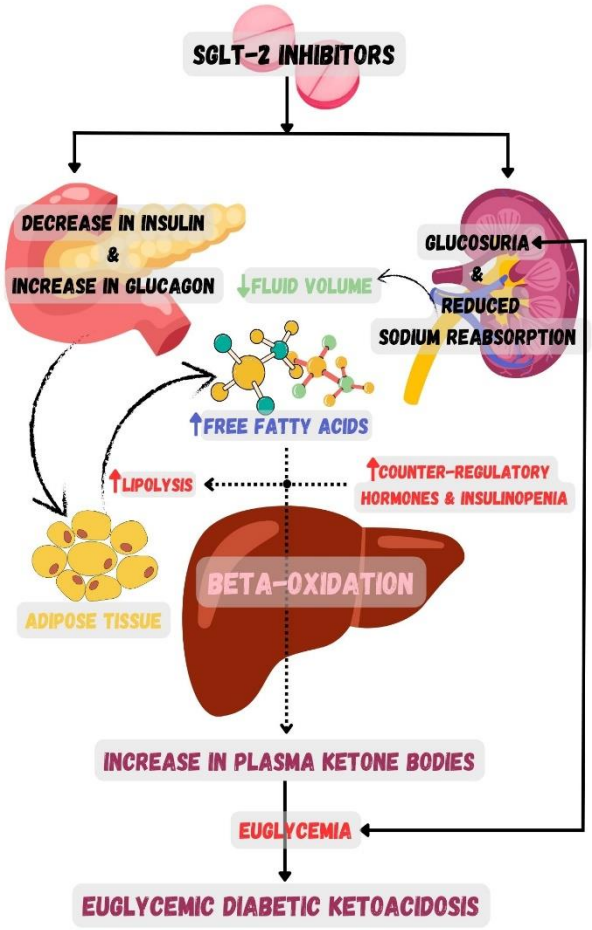

Figure 1: SGLT2 inhibitors induced euglycemic diabetic ketoacidosis

4. Investigation and Diagnosis:

For patients presenting with symptoms of Diabetic ketoacidosis, these are the following initial investigations are to be made.

- Full blood count [Hemoglobin level, WBC, RBC, MCV, MCH, Platelets]
- Bone profile that includes [albumin, calcium, alkaline phosphatase]
- HbA1C level
- Liver function test
- Urea and electrolytes [2,6]
- Venous blood gas
- Serum and urine ketones
- β-hydroxybutyrate [27,31]
- Renal function test [6]
- Electrocardiogram and Blood Pressure
- Anion gap
- Bicarbonates [17,14,27]
- Serum PH
- Serum glucose
- Chest radiograph
- Arterial blood gas
- Serum potassium
- Mental status (Alert, drowsy, stupor or coma) [27,31]

The American Diabetes Association (ADA) explains DKA as glucose level more than 250mg/dl, PH less than 7.3, serum bicarbonate level less than 18mmol per liter, anion gap more than10-12 and the presence of ketones in blood/urine [27,29,30].

The American college of endocrinology suggests that serum PH and β-hydroxybutyrate can be used as a diagnostic tool in the assessment of Diabetic ketoacidosis. [6] Investigation of patient, resulting with increased blood glucose level, increased blood ketones such as β-hydroxybutyrate, serum acetone and increased urine ketones as well are diagnosed as diabetic ketoacidosis. [8] Patients presenting with PH less than 7.30, Bicarbonate less than 18meq/l and increased anion gap are assessed with Diabetic ketoacidosis. [6,2,27] The range of Serum β-hydroxybutyrate more than 3mmol/l in pediatrics and more than 3.8mmol/l in adults and Anion gap less than 12mmol/l are reliable for diagnosing diabetic ketoacidosis in patients. [6,2,27,29]

As per UK guidelines, glucose level more than 200mg/dl, PH less than 7.3, bicarbonate less than 15mmol/L, presence of ketones in urine/blood can be diagnosed as Diabetic ketoacidosis. [8,27,28] Anion gap is an important parameter to be calculated in diagnosing DKA. It must be calculated in each patient and if its range is more than 20meq/l which can occur due to increased productions and elevated levels of β-hydroxybutyrate and acetoacetic acid. Both β-hydroxybutyrate and acetoacetic acid are negatively charged and they can lead to increased anion gap. [27] Diagnosis of DKA can be challenging in patients with chronic renal failure due to underlying Acid-base imbalance and metabolic acidosis. In this type of patients DKA can be diagnosed, if anion gap is more than 20. [29]

5. Diagnostic criteria:

Diagnostic criteria for assessing Diabetic ketoacidosis in patients includes:

- Patients with Relative euglycemia lower than 250mg/dl. [6]
- Acidosis with pH lower than 7.30 and serum bicarbonate lower than 18meq/l. [6]
- Patients presenting with ketosis {preferably increased β-hydroxybutyrate, serum acetoacetate and urine ketones. [6]

The diagnostic criteria for assessing SGLT2i induced DKA includes:

- Moderate hyperglycemia less than 300mg/dl. [8]
- Metabolic acidosis with increased anion gap. [8]
- Increased blood ketones/ urine ketones. [8]

5.1 Differential diagnosis:

The differential diagnosis for assessing Diabetic ketoacidosis includes;

1. Patients with new onset of Type-1 Diabetes mellitus. [2]
2. Euglycemic DKA related to SGLT2i. [2]
3. Occurrence of metabolic acidosis and high anion gap due to alternative cause. [2]
4. Ketoacidosis caused by alcohol consumption.[4]
5. Patients with chronic liver disease. [4]
6. Ketosis due to starvation. [4]
7. Patients with Glycogen storage disease. [4]

6. Prevention:

- Immediate withdrawal of SGLT2i in patients who are scheduled to undergo major surgery. SGLT2i should be stopped atleast 3 days before surgery. [3,4,8,18,20,30,31]
- If the patient is taking SGLT2i then he/she should be explained about the risk factors of DKA. [4]
- SGLT2i should be stopped in patients who are hospitalized due to serious illness/Chronic diseases. [3]
- Instead of SGLT2i insulin can be used in patients presenting with other predisposing risk factors of Diabetic ketoacidosis. [3]
- SGLT2i should be stopped immediately if the patient is suspected or confirmed with DKA induced by SGLTi and it should not be started without identifying and resolving another cause for ketoacidosis. [3]
- If SGLT2i is prescribed in Type 1 DM then the patient should be closely monitored. [4]
- Patient should be advised about Carbohydrate intake. [4,31]
- Patients with type 1 and type 2 DM are to be counseled about life style modifications.[4]
- Patient education about withdrawal of SGLT2i during fasting, illness, excessive alcohol intake and prolonged exercise. [4,28,31]
- Patient should be educated about usage of insulin and supplemental short acting insulin during infection /fever and illness. [29]
- Ketosis and Metabolic acidosis are the key requirement for diagnosing DKA. SGLT2i therapy should be stopped, if DKA is assessed using following parameters such as PH, serum ketones/bicarbonate and anion gap. [28]

- Treatment with IV insulin and glucose in DKA patients should be closely monitored for anion gap, arterial PH and serum β-hydroxybutyrate. [31]

7. Treatment:

Once DKA has been diagnosed in patients, treatment should be started as soon as possible according to local protocols and through recommendations of guidelines.

The therapeutic goal of DKA treatment includes managing of;

1. Hyperglycemia
2. Electrolyte imbalance
3. Metabolic acidosis
4. Ketoacidosis
5. Volume status
6. Other precipitating factors. [29]

Successful management of DKA requires treating of metabolic acidosis, anion gap and correction of electrolyte imbalance & dehydration. [4]

The recommendations for primary treatment of DKA suggests,

7.1 Fluid Therapy

Management of Volume restoration with Iv fluids such as isotonic saline (Nacl-0.9%) and correction of metabolic acidosis. [2,3,4,29] Patient should be closely monitored with glucose and ketones level. [2] Depending on patient's clinical presentation and fluid status, intravenous hydration can be provided to combat osmotic diuresis. [5] If the patient is taking SGLT2i, then he/she may have Blood glucose level lower than expected, so they may need more IV glucose initially. [5] Since metabolic acidosis increases with hydration alone, IV insulin should not be administered. [2] Discontinue SGLT2i immediately if DKA is confirmed and do not restart until another for DKA is identified and resolved. [2,3] Before administering insulin, ensure that patients potassium level is >3.3 meq/l. [3,29]

7.2 Insulin Therapy

In patients with DKA insulin can be administered through intravenous infusion which is the preferred route of insulin therapy in DKA patients. [29] Treatment of DKA includes providing of insulin and intravenous glucose with administration of insulin through intravenous infusion. [5] Start with continuous IV infusion of insulin administration and when metabolic acidosis is corrected and acid-base balance is restored, change it to intensive subcutaneous regimen. [3] Consider about additional glucose infusion at the starting of therapy. [3] In DKA patients, IV insulin can be given at a fixed dosage regimen of 0.1U/kg/hour to treat ketoacidosis. [18,29] The American Diabetes Association suggests that IV insulin therapy can be given with or without insulin bolus along with considering the patient's serum potassium range more than 3.3meq/l. [29] Insulin Aspart and insulin Lispro can be administered subcutaneously for every 1-2 hours which is considered to be safe and efficient and given as a continuous insulin infusion therapy in intensive care unit (ICU). [29]

7.3 Bicarbonate, Potassium and Phosphate Replacement

According to recommendations of ADA Guidelines, infusion of Bicarbonate can only be considered in-case of life-threatening metabolic acidosis with PH level of 6.9 or less. [3,29] Make sure that proper ventilation is achieved during bicarbonate infusion to avoid intracellular acidosis. [3] Administer Bicarbonate if PH of patient is less than 6.9. [3] In case of Bicarbonate administration, consider administration of calcium through IV in order to prevent fall in ca^{2+}. [3] During DKA management, serum potassium level should be monitored closely. Insulin therapy should be stopped if serum potassium level reduces below 3.3meq/l. If hypokalemia occurs, it may lead to cardiac arrest and arrhythmias. [29] Serum phosphate level will decrease in DKA during insulin therapy. Studies showed over 90%

of patients developed hypophosphatemia during insulin and fluid therapy. Depending on phosphate deficiency, initial therapy for hypophosphatemia includes infusion of potassium phosphate with a dose of 0.1-0.2mmol/kg for 6 hours. Close monitoring of calcium and phosphorous levels is suggested because hypocalcemia may occur due to phosphate replacement. Patients with chronic renal failure/renal insufficiency or hypocalcemia may require less phosphate replacement. [29]

8. Conclusion:

From the above-mentioned information's, we come to know that the SGLT2i are now commonly utilised in diabetic patients to manage hyperglycaemia. These drugs are receiving greater attention in diabetes therapy, owing to recent research demonstrating Cardiovascular, weight reduction and renal advantages. Euglycemic DKA could be misdiagnosed and hence the practitioners should be cautious in identifying eDKA by carefully assessing patients, particularly if the individual is present with Fatigueness, stomach pain, nausea and vomiting resulting in reduced blood pressure and dehydration, altered psychological condition, for acidosis and testing urine ketones even in normal ranged blood glucose levels. If eDKA is suspected in individuals with SGLT2i therapy, immediate therapy with intravenous fluids and insulin must be started in affected individuals, once the precipitant drug is withdrawn. Patient counselling on precipitating factors, reason for occurrence, clinical manifestations are crucial, whereas the patients should also be counselled to undergo urine dipstick tests to assess for ketones and recommended to consult a doctor before making any dietary changes or if they experience any discomfort, and to receive medical attention right away if the dipstick test result is positive. Further more research is required to fully comprehend the mechanism of eDKA in the presence of precipitants and however various intensive research to be conducted for further conclusion.

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Conflict of interest:

There is no conflict of interest between the authors.

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