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Diabetes Ketoacidosis Is a Cause of Concern in Sodium-Glucose Co-Transporter-2 Inhibitors Medication

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Abstract: Diabetic ketoacidosis (DKA) is a dangerous complication that can afflict persons with Type 1 and Type 2 diabetes and is caused by a lack of glucose utilization and insulin generation. DKA is diagnosed by observing the anion gap values, blood glucose level, pH, serum bicarbonate level, and so on. DKA is associated with an elevated blood glucose of > 250 mg/dl (16.7 mmol/l) and is diagnosed by observing the values of anion gap, blood glucose level, pH, serum bicarbonate level, and so on. It occurs more frequently in type 1 diabetics with low insulin levels. Sodium-glucose Co-transporter-2 (SGLT-2) inhibitors are a novel family of anti-diabetic medications that lower blood glucose levels and produce glucosuria. The US Food and Drug Administration (USFDA) has issued a drug safety warning about the increased risk of DKA when using SGLT-2 inhibitors. Following the USFDA's warning, the European Medicine Agency reported 101 more cases of ketoacidosis caused by SGLT-2 inhibitors in people with Type 2 Diabetes Mellitus (EMA). According to the American Association of Clinical Endocrinologists, all SGLT-2 inhibitors should be stopped 3-4 days before major surgery and 24 hours before elective surgery. This review article focuses on the metabolism of ketone bodies and many pathophysiologic mechanisms of SGLT-2 inhibitors, which lower insulin/glucagon ratios, promote glucagon secretion from alpha cells, and increase ketones levels by stimulating lipolysis and resulting in ketogenesis. The primary goal of this study is to improve our understanding of a significant consequence of DKA caused by sodium-glucose cotransporter-2 inhibitors in patients with Type 1 and Type 2 diabetes. Psychosocial factors linked to diabetic ketoacidosis in adults with type 1 diabetes, as well as the prevalence of DKA in COVID-19 patients, have been linked to higher severity of mortality and duration of stay in these patients, according to recent research.

Key Words: Diabetes Ketoacidosis, Sodium-Glucose Cotransporter-2 Inhibitor, Ketogenesis, Type-1 Diabetes, Type-2 Diabetes.

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1. INTRODUCTION

Diabetic ketoacidosis is a condition that can affect both type 1 and type 2 diabetes patients. It is most common in type 1 diabetes patients when our bodies use fatty acids instead of glucose as an alternate energy source due to a lack of insulin. Hyperglycemia, metabolic acidosis, and hunger are all linked to ketosis. When there is a lack of insulin, or the person is fasting for an extended period, the body produces acid called ketones instead. DKA is related to a blood glucose level of > 250 mg/dl (16.7 mmol/l) [1,4], which is caused by a lack of glucose utilization and insulin synthesis. The phrase "euglycemic diabetic ketoacidosis" refers to when blood glucose levels of 200 mg/dl (11.1 mmol/l) are either moderately elevated or normal[1, 5]. A novel family of anti-diabetic medications known as SGLT-2 inhibitors has been introduced to treat type 2 diabetes by producing glucosuria, which lowers blood glucose levels. By inhibiting the sodium-glucose cotransporter channel found in PCT in nephrons, it restricts glucose and sodium reabsorption into plasma[5, 6]. Ketoacidosis has recently been diagnosed in both Type-1 and Type-2 diabetes patients after taking SGLT-2 inhibitors. The Food and Drug Administration (FDA) in the United States has published a drug safety message warning of an elevated risk of DKA after using SGLT-2 inhibitors. Following the FDA's warning, the European Medicine Agency (FMA) reported 101 cases of DKA related to Type-2 Diabetes Mellitus[6,7]. The formation of ketoacidosis, several pathophysiologic mechanisms by which SGLT-2 inhibitors trigger ketoacidosis, case reports of SGLT-2 inhibitors inducing DKA in patients with Type 1 and Type 2 diabetes, and how we can overcome this concern by looking at some preventive strategies will all be discussed in this review.

1.1 Ketogenic Pathway

DKA is a life-threatening condition caused by a shortage of insulin and an increase in counter-regulatory hormones such as glucagon, which produce hyperglycemia and contribute to the generation of ketones. Put another way, every time we eat food, our blood glucose level rises, and our pancreas responds by generating insulin from beta cells. As a result, insulin can regulate glucose in other body regions, including the liver, fatty tissues, and muscles, which rely on glucose for energy. The human body requires energy, which we obtain from our food. Food carbohydrates are broken down into glucose. Suppose our bodies cannot produce insulin (type-1 diabetes) or are insulin-resistant (type-2 diabetes). In that case, our bodies go through a metabolic shift known as insulinopenia, in which our bodies use fat instead of glucose as an energy source. By beta-oxidation, the breakdown of fat (lipolysis) produces a chemical called ketone, and the increased quantity of ketone causes our blood to become acidic. Ketones are acidic, and when they are created in the body, they lower the pH, resulting in DKA. Diabetes ketoacidosis is a significant complication that can occur as a result of this. When our body uses free fatty acids instead of carbohydrates for energy, ketone bodies such as Acetoacetate, acetone, and beta-hydroxybutyrate are produced. Fatty acids are converted to Acetoacetate and beta-hydroxybutyrate during the ketogenesis process. Fatty Acids are converted to ketone bodies in the liver through beta-oxidation. Ketoacidosis is caused by synthesizing Acetyl CoA from fatty acids and glucose[8] (Figure-1).

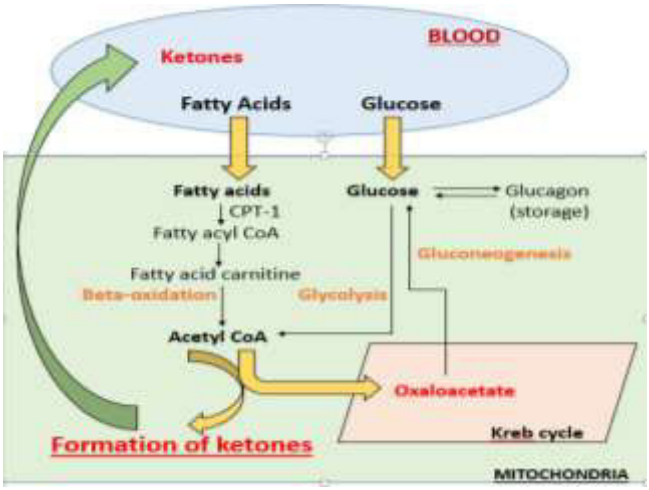

Fig-1: Formation of Acetyl-coA from Fatty acids and glucose leads to Ketosis[8]

Transport of fatty acyl CoA to fatty acid carnitine in the presence of an enzyme, carnitine palmitoyltransferase-1 (CPT-1), can result in ketone bodies, which is a crucial step in the process of fatty acid beta-oxidation to Acetyl CoA. Acetyl CoA is produced by a) glucose glycolysis or b) fatty acid beta-oxidation. Acetyl CoA can either participate in the kerb cycle with oxaloacetate or cause ketones to develop. When acetyl CoA enters the metabolic cycle for the first time, it reacts with

oxaloacetate. Pyruvate is converted to oxaloacetate during glycolysis. When a person is fasting or not producing insulin (diabetes), there is a lack of glucose production and no glycolysis process. More oxaloacetate is produced instead of Acetyl CoA being condensed. It's used in the production of gluconeogenesis. The acetyl CoA is thus redirected away from the kerb cycle and toward the ketogenesis pathway[8]. Variations in insulin and glucagon hormone concentrations are critical in the production of ketones. The concentrations of insulin and glucagon hormones can determine whether Acetyl CoA will enter the ketogenic pathway or not[9].

a) High insulin inhibits the synthesis of ketone bodies because insulin has antilipolytic action (Figure 2), which indicates that insulin acts by raising the activity of acetyl CoA carboxylase, which produces malonyl CoA, which is an inhibitor of the carnitine palmitoyltransferase1 enzyme. When the CPT-1 enzyme is blocked, no fatty acyl CoA is transferred to fatty acid carnitine, and ketoacidosis is prevented.

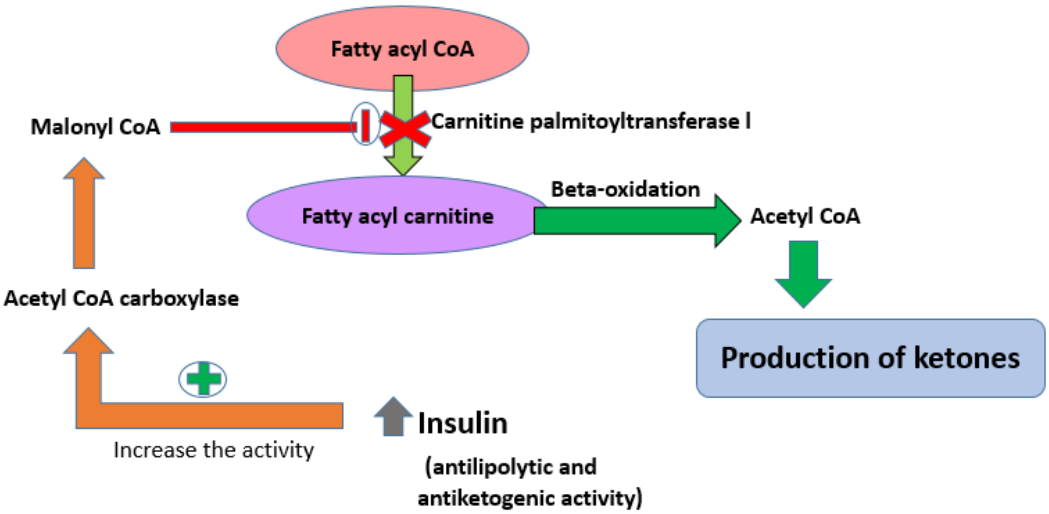

Fig 2: High insulin level shows its antilipolytic and antiketogenic activity[9].

Insulin works by raising the activity of the enzyme acetyl CoA carboxylase, which produces malonyl CoA, an inhibitor of the carnitine palmitoyltransferase-1 (CPT-1). As a result, the transport of fatty acyl CoA to fatty acid carnitine is blocked when the CPT-1 enzyme is inhibited, and further ketoacidosis is prevented[5,10].

1.2 A situation characterized by high glucagon levels and low insulin levels.

Elevated glucagon levels directly influence the production of ketone bodies. The glycogenolysis process and the beta-oxidation of fatty acids to ketones are accelerated by glucagon.

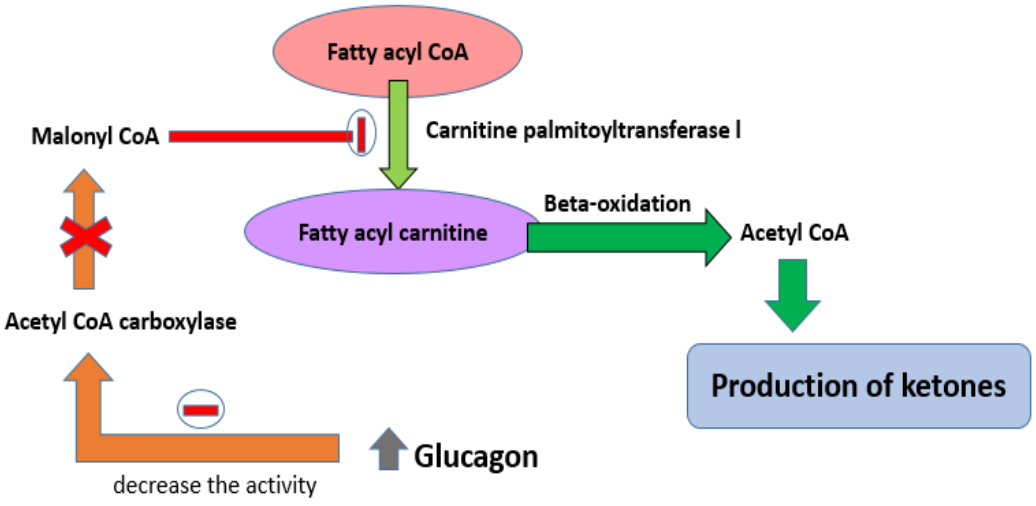

Fig-3: High levels of glucagon lead to the formation of ketones in mitochondria[10].

Low levels of the malonyl-CoA enzyme, which normally inhibits CPT-1, which is formed by acetyl carboxylate, are caused by high glucagon levels. CPT-1 prevents the transesterification of fatty acyl CoA to fatty acid carnitine once it is blocked. As a result, when glucagon levels are high, there is no synthesis of malonyl CoA and no inhibition of CPT-1. As a result, it promotes fatty acid transport from CoA to carnitine, and an elevated level of fatty acid carnitine leads to beta-oxidation and the formation of ketone bodies[7,10] (**Figure-3)**. As a result, ketosis arises in the mitochondria, and we can deduce that insulinopenia and hyperglucagonemia cause diabetic ketoacidosis.

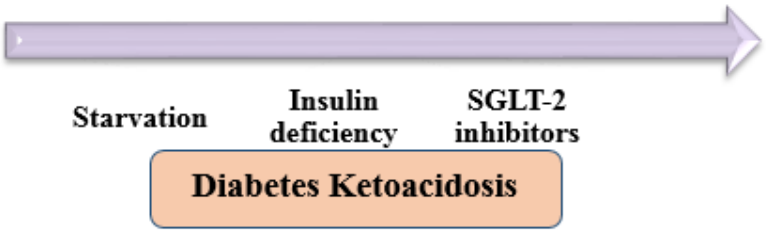

Fig-4: Contributing Factors of Ketoacidosis[10]

1.3 Ketoacidosis is caused by several reasons, including

1) Starvation can cause non-diabetic ketoacidosis. Because our systems utilize fat, a low-carbohydrate diet can kickstart ketosis.

2) Insulinopenia can lead to DKA since insulin is the hormone that governs glucose transport to other parts of the body so that it can be used. 3) SGLT-2 inhibitors act by boosting the glucagon hormone, increasing ketone reabsorption and causing continuous glucosuria, which leads to ketone production (Figure-4) and inhibiting the sodium-glucose cotransporter channel[10].

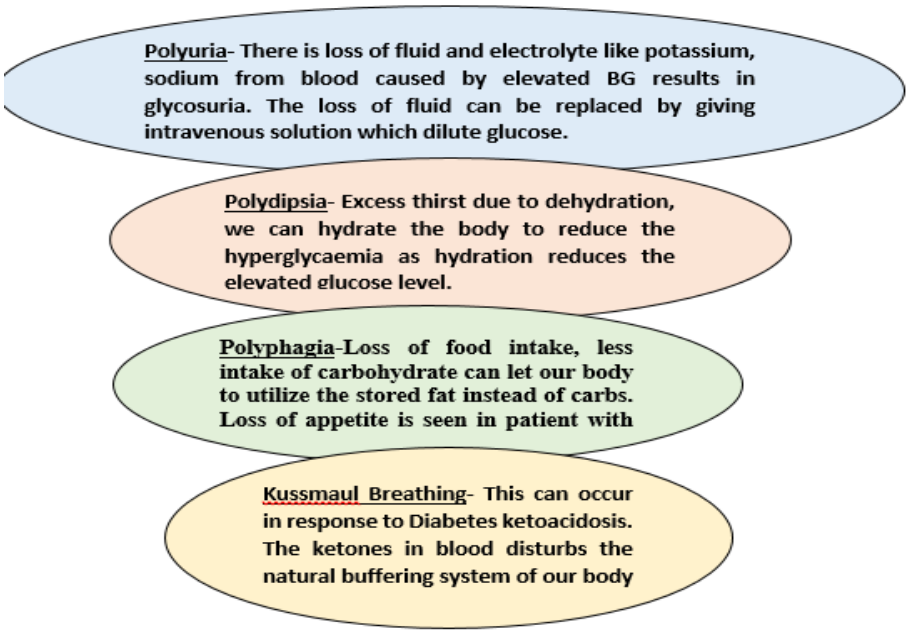

Fig : Signs and symptoms of DKA (characterized by hyperglycaemia

1.4 SGLT-2 inhibitors trigger Diabetes Ketoacidosis

Some evidence suggests that sodium-glucose co-transporter-2 inhibitors enhance glucagon secretion when given. These "gliflozins," such as dapagliflozin, canagliflozin, ipragliflozin, and empagliflozin, have been shown to cause hyperglucagonemia by activating alpha cells and lowering insulin production. As previously mentioned, if glucagon levels are high for any cause, glycogenolysis, lipolysis, and fatty acid oxidation to ketones occur. Because glucagon inhibits acetyl CoA carboxylase, its overexpression directly impacts ketone body production. Because malonyl CoA is not produced, the CPT-1 enzyme in the liver increases, resulting in fatty acid carnitine and ketone overproduction[5, 7]. Because these medicines can lower insulin levels, even more, they should be used with caution in individuals who have reduced insulin secretion due to beta-cell insufficiency or who have a history of diabetes. The presence of SGLT-2 transporters in the pancreas' alpha cells has been

suggested as an alternative explanation for glucagon's rise. Previously, SGLT-2 was only found in renal tubule PCT, but recent research has shown the SGLT-2 transporter in alpha cells. Dapagliflozin inhibits the transporter while simultaneously stimulating glucagon secretion from human islet alphaTC19 cells when administered. As a result, we can deduce that there are medications available that were designed to lower glucose levels but instead elevate blood glucose, reducing their efficacy[11]. To fully understand how inhibition of alpha-cell SGLT-2 is linked to glucagon release, more clarity and research are needed.

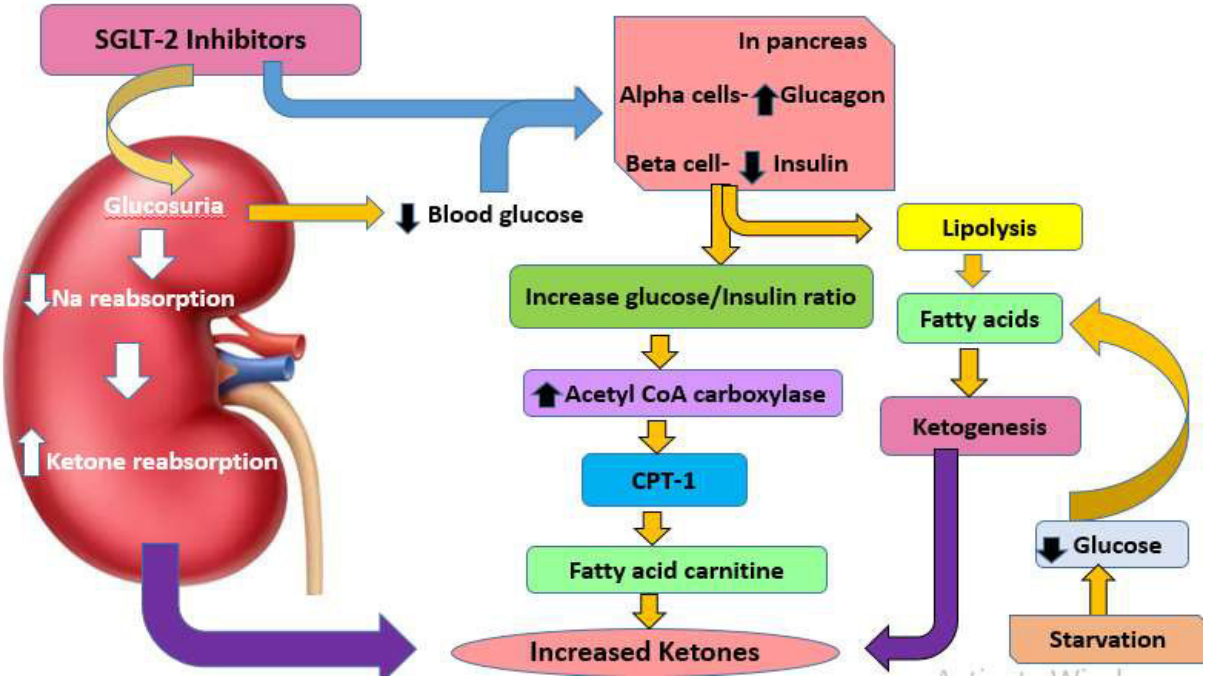

Fig-5: Various mechanisms of SGLT-2 inhibitors lead to the promotion of ketoacidosis[11]

SGLT-2 inhibitors promote ketoacidosis through various pathways, including a) SGLT-2Inhibitors in the kidney-Glucosuria, b) In the pancreas-stimulating alpha cells, and c) Starvation promotes a metabolic shift to lipids and the synthesis of ketones. The pancreas's alpha cells are associated with the rise in endogenous glucose production (EGP) caused by SGLT-2 inhibitors. According to several pieces of research, glucagon has a function in stabilizing blood glucose levels in hypoglycemia by raising EGP when renal reabsorption is limited. Though we all know, SGLT-2 inhibitors cause glucosuria, lower blood glucose levels, and activate alpha cells in response to hypoglycemia by releasing glucagon, which raises EGP and leads to the generation of ketone bodies. Gluconeogenesis and glycogenolysis, in contrast to glucosuria, raise the glucose level further[11] (**Figure 5**).

1.5 Mechanism of Sodium-glucose co-transporter-2 inhibitors associated with DKA

Inhibitors of the sodium-glucose co-transporter-2 cause Diabetes Ketoacidosis through several different mechanisms

1. When SGLT-2 inhibitors are taken, they lower insulin secretion, which leads to enhanced lipolysis and fatty acid oxidation in the liver. In addition, these medicines stimulate counter-regulatory hormones like glucagon, adrenaline, and others, increasing glucose levels. To establish glycaemic regulation, insulin levels and counter-regulatory hormones like glucagon must be balanced, as all CRH oppose insulin's activity and increase the glucagon/insulin ratio while decreasing circulating insulin, resulting in ketogenesis[5, 12]. In addition, SGLT-2 transporters are found in the alpha cells of the pancreas, and glucagon release is increased when sodium-glucose cotransporters are blocked, which simulates hypoglycemia (Figure 5).

2. The primary goal of SGLT-2 inhibitors was to impede glucose reabsorption and cause glucosuria. However, it has been discovered that inhibiting the SGLT-2 transporter causes ketones to be reabsorbed (Figure 5). As a result, SGLT-2 inhibitors impede sodium reabsorption in PCT, resulting in a rise in sodium concentration in DCT. As a result, the electrochemical gradient promotes ketone body reabsorption from sodium monocarboxylate transporter-1 as it exits the renal tubular epithelium. The patient does not experience ketonuria because the ketone bodies are reabsorbed, but they still have ketoacidosis. If the patient suspects they are suffering from ketoacidosis, they must be tested for plasma ketones rather than urinary ketones in addition to the arterial pH test.

3. There is an oversupply of ATP in the kidney as salt reabsorption in the proximal convoluted tubule is diminished. This combination of extra ATP in the kidney and decreased ATP consumption in PCT causes the kidney to divert away from metabolic pathways that normally create ATP, such as ketone body oxidation and monogenesis, resulting in the indirect loss of $NAHCO_3$ from PCT, aggravating metabolic acidosis. PCT changes when the sodium-glucose cotransporter is inhibited. Aside from that, SGLT-2 is linked to diabetic ketoacidosis and can be caused by prolonged fasting (starvation) or stress[13] (**Figure 5**).

1.6 Metformin and SGLT-2 inhibitors as a combination therapy

The FDA has approved a fixed combination dose of any sodium-glucose cotransporter-2 inhibitor (Canagliflozin, dapagliflozin, and empagliflozin) with Metformin. Metformin is the first-line pharmacological therapy for Type-2 diabetes patients because of its excellent efficacy in glycemic control. Clinical recommendations recommend SGLT-2 inhibitors as an add-on therapy with Metformin for patients unable to reach a normal glucose level with Metformin. Patients with higher HbA1c levels are now offered combination therapy instead of monotherapy; SGLT-2 Inhibitors have a strong reducing impact, resulting in a drop in plasma glucose levels and glucosuria. As previously mentioned, the sodium-glucose cotransporter-2 protein is also found in pancreatic alpha cells. As a result, using SGLT-2 inhibitors enhances glucagon secretion and hepatic gluconeogenesis. Metformin, on the other hand, operates by blocking gluconeogenesis. Hepatic gluconeogenesis, renal glue reabsorption, and the development of glucosuria are all inhibited by this combination. When metformin and SGLT-2 inhibitors are used together, glycemic control improves.

Nonetheless, some investigations[15] have found a link between this combined antihyperglycemic medication and an increased risk of metabolic acidosis. Dizon et al. described a case of a 45-year-old man[16]. This person has type 2 diabetes and is on Metformin and a biphasic insulin mix of 26 units twice daily. Canagliflozin 300 mg was added, but it was later removed due to insulin titration. Eighteen months after starting this medicine, he developed shortness of breath and metabolic acidosis. IV fluids and an insulin drip were administered later for therapy. A 51-years old male with Type-2 diabetes was treated with Metformin and afterwards given dapagliflozin, according to Chow[17]. With a pH of 6.8, a blood glucose level of 22 mmol/L, and ketones of 6 mmol/L, he was taken to the hospital with myocardial infarction and diabetes ketoacidosis.

1.7 Types of SGLT-2 Inhibitors which are associated with DKA

The first SGLT-2 inhibitor, canagliflozin, was licenced by the US Food and Drug Administration in 2013, followed by empagliflozin and dapagliflozin in 2014. These medications became popular in the market earlier due to their mode of action in decreasing blood glucose and their weight loss effect. However, twenty cases of DKA were later brought to light due to adverse event reporting. Patients with type 2 diabetes who took canagliflozin, dapagliflozin, or empagliflozin experienced diabetic ketoacidosis. In 2010, 142,000 people with diabetes ketoacidosis were hospitalized, with 23% having type-2 diabetes. According to the author, there were 450 cases of DKA associated with canagliflozin use in 2017, 144 cases associated with dapagliflozin use, and 46 cases associated with empagliflozin use in 2017[18].

1.7.1 Canagliflozin

There are estimated incidences of 0.52 and 0.76 per 1,000 patient-years in patients using canagliflozin 100 and 300 mg dosages, respectively. In 2017, there were 450 instances of DKA in people aged 18 to 87, with 215 females, 158 males, and 67 people of unknown gender. A total of 189 cases were reported as an off-label usage of canagliflozin, with 30 cases having ketoacidosis[18]. After using 100 and 300 mg canagliflozin, up to 9.4 per cent of type 1 diabetic patients had DKA.

1.7.2 Dapagliflozin

DKA was reported in 144 people aged 16 to 86, including 86 females, 46 males, and 13 unclear genders. One hundred one people did not have insulin in their system, according to the 144 reports. Dapagliflozin was used off-label in 46 of them, and 18 were found to have ketoacidosis.

1.7.3 Empagliflozin

There were 46 cases of DKA in people aged 18 to 71 years after using empagliflozin, with 27 females and 19 males. 17 of the 46 people were on insulin, while 29 were not[18]. Peter D. Farjo reported on a case in 2016[19]. A 57-year-old type-2 diabetes patient was admitted to the hospital after taking empagliflozin alone for 189 days. He was diagnosed with DKA, and his HbA1c level dropped from 53 to 39 mmol/mol in the first three months. He was also on a reduced carbohydrate diet for four months. It was also discovered that this patient had begun taking krill oil capsules within the last two weeks. The report revealed a bicarbonate level of 13 mmol/l, a BG of 120 mg/dl, an anion gap of 26 mmol/L, and ketones of 8.1, indicating ketoacidosis. Providers should strongly advise patients about the potential negative effects of SGLT-2 inhibitors before taking them.

1.8 Other adverse effects of sodium-glucose cotransporter-2 inhibitors

1. Genital mycotic infection, urinary tract infection, hypoglycemia, and volume depletion are the most common side effects.

2. Adverse consequences that are less common: Diabetes ketoacidosis, lower limb amputation (induced by canagliflozin), bladder cancer (produced by dapagliflozin), and kidney injury are all possible side effects of dapagliflozin[20].

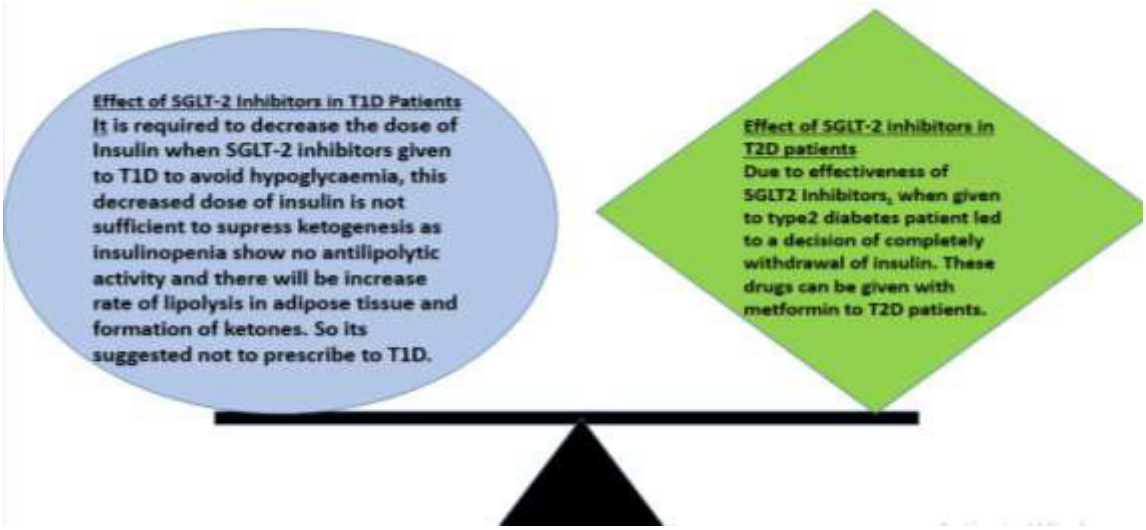

Fig-6: ***Effect of SGLT-2 Inhibitors in Type-1 and Type-2 Diabetic Patients***[20]

When SGLT-2 inhibitors are used to treat type-1 diabetes, a ketosis-promoting mechanism is identified, even though these medications are not FDA-approved to treat type-1 diabetes. Therefore, while it is legal to administer these medicines to type 2 diabetes patients as SGLT-2 inhibitors, they should be used with caution[20] (Figure-6).

1.9 A case report of SGLT-2 inhibitor-induced DKA in a Type-1 diabetic patient

Three hundred fifty-one patients with type 1 diabetes were examined for 18 weeks with SGLT-2 inhibitors and a placebo in a case study by Goldenberg[21]. Canagliflozin was given in two doses, one of 100 mg and the other of 300 mg. Patients receiving canagliflozin had their insulin dose lowered by 10% to 20%. The data revealed that both canagliflozin-treated individuals were diagnosed with DKA, but none of the placebo-treated patients was diagnosed with DKA. SGLT-2 inhibitors are now administered off-label for type-1 diabetic patients due to their extra-glycaemic effects. The European Medicines Agency and the FDA Adverse Event Reporting System (FAERS) do not suggest SGLT-2 inhibitors for insulin-dependent patients[14, 22, 23].

1.10 A case report of SGLT-2 inhibitors causing DKA in a Type-2 diabetic patient

According to Redford, there was case[24]. Because her HbA1c was 54 mmol/mol and there were no signs of ketones at the time, a 58-year-old lady with type-2 diabetes was prescribed Metformin. When she showed no improvement, the doctor prescribed dapagliflozin 10 mg once daily with Metformin. After a few days, her blood glucose levels dropped dramatically, which was attributed to the down titration of insulin. As a result, her general practitioner advised her to stop using insulin and closely monitor her blood sugar levels. She was diagnosed with DKA with 5.1 mmol/l of ketones, 30.8 mmol/l of blood glucose, and a pH of 6.84 due to insulin withdrawal. We can conclude from this example that more caution should be exercised while administering SGLT-2 inhibitors and that it may be harmful to withdraw insulin from type-2 diabetes patients in some circumstances. The FDA Adverse Event Reporting System received 20 reports of DKA caused by SGLT-2 inhibitors. The prevalence of DKA in COVID-19 patients has been connected to a higher degree of mortality and length of stay in these patients, according to recent review papers published in 2021. Despite having no medical history, we present the case of a patient who arrived with COVID-19 symptoms and was determined to be in DKA. The underlying pathophysiology of this illness is highlighted in the case report. This example highlights the importance of being vigilant and cautious while treating patients with both COVID-19 and DKA, as these patients are at a higher risk of dying. Furthermore, the mechanism of COVID-19-induced ketosis remains unexplained, necessitating additional research.

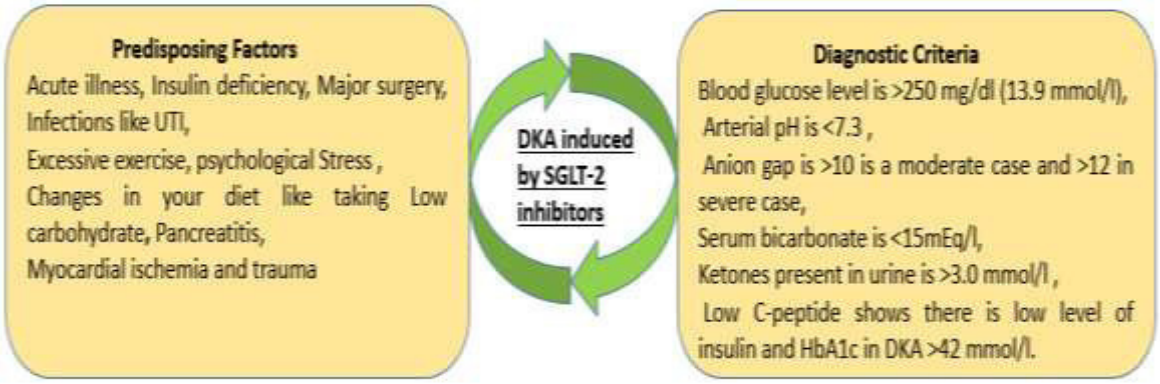

Fig-7: ***Diagnostic criteria and precipitating factors of DKA***[25,26]

Ketoacidosis is linked to predisposing circumstances, including acute sickness (infection, surgery) and a low-carbohydrate diet in patients using sodium-glucose cotransporter-2 inhibitors. In addition, there have been reports of a predisposing factory "procedure" linked to DKA in people taking SGLT-2 inhibitors. Figure 7 shows a few more predisposing factors. Hine *et al.*[5, 14] described a case of diabetic ketoacidosis in a 36-year-old woman who had a distal pancreatectomy and had been diagnosed with type-2 diabetes. She experienced DKA with a blood glucose level of 106 mg/dl just 24 hours after switching from insulin to dapagliflozin. Peters *et al.* describe another example of surgery associated with DKA[2]. Two patients with Type-2 Diabetes underwent surgery, one with a spinal sigmoid colectomy and the other with a cervical foraminotomy. Canagliflozin was prescribed to both of them. With blood glucose levels of 200mg/dl, both patients developed DKA. According to the American Association of Clinical Endocrinologists, all SGLT-2 inhibitors should be stopped 3-4 days before major surgery and 24 hours before elective surgery. SGLT-2 inhibitors have a half-life of 11 to 13 hours. The effects of SGLT-2 inhibitors can last for many days after they are stopped, and patients may still have glucosuria and ketonemia[25, 26]. The development of diabetes ketoacidosis after administration of SGLT-2 inhibitors has been described in the following five patient case studies.

1. Hayami *et al.* published a case study on a patient[27] 32-year-old woman with increased Blood Glucose (191 mg/dl) and a reduction in c-peptide (0.4 g/day), urinary ketone bodies (3.4 mmol/l), pH (5), and $NaHCO_3$ (3 mmol/l). DPP4 inhibitors and Metformin were initially prescribed, but Ipragliflozin (50 mg/day) was eventually prescribed. DKA developed after thirteen days of Ipragliflozin treatment. Possible causes include following a rigorous low-carbohydrates diet, which lowers circulating insulin levels and causes a metabolic shift in the body, resulting in more ketone bodies. IV Insulin and glucose were infused into the patient. C-peptide excretion in urine was increased (40.2 g/day) after therapy.

2. Maruthappu *et al.*[28] reported a 34-year-old male with Type-2 diabetes, pH (6.9), urine ketone bodies (7.8, normal 0.6 mmol/l), and $NaHCO_3$ (14.9 mmol/l) in his urine. SGLT-2 inhibitors are a type of prescription medication (dapagliflozin). The signs and symptoms of metabolic acidosis have been recorded, and the treatment includes IV insulin and glucose.
3. A 36-year-old woman with a medication taking dapagliflozin was reported by Maruthappu *et al.*[28] in another Patient Case Study. Ketoacidosis has been Diagnosed with elevated urinary ketone bodies (15.6 mmol/l), pH 7.3, serum bicarbonate (19.9 mmol/l), and normal blood glucose level (5.9 mmol/l).

4. ***Patient case study #4***

In 2020, Wang *et al.*[25] reported a case of a 40-year-old woman who had diabetic ketoacidosis with a high-anion gap following empagliflozin therapy. The last dose of empagliflozin was given 18 hours before surgery. A severe high-anion gap was discovered with ketones of 7.7 mmol/l and $NaHCO_3$ of 10 mmol/l. After being diagnosed with DKA, she was treated with IV insulin and glucose.

5. ***Patient case study #5***

Redford *et al.*[24] described the case of a 58-year-old lady whose blood glucose level fell within 36 hours of the last insulin dosage. 10 mg of dapagliflozin per day was prescribed, but it was advised to discontinue using insulin and solely take dapagliflozin. The presence of ketone bodies (5.1 mmol/l), bicarbonates (5.6 mmol/l), and a sudden drop in pH (6.9) was noticed.

Table 2: Diabetic ketoacidosis (DKA) with SGLT2 inhibitors in type 2 diabetes

S. N.	Author	Source	DKA seen	Drug	Drug Patient profile	Background reasons
1	Hayami *et al.*	*Lancet Diabetes Endocrinol.*2015	1	DPP4 inhibitors and Metformin were initially prescribed, but Ipragliflozin (50 mg/day) was eventually prescribed. Unfortunately, DKA developed after thirteen days of Ipragliflozin treatment.	A 32-year-old woman with increased Blood Glucose	Possible causes include following a rigorous low-carbohydrates diet, which lowers circulating insulin levels and causes a metabolic shift in the body, resulting in more ketone bodies.
2	Maruthappu *et al.*	*Med Clin North Am.* 2017	1	dapagliflozin	34-year-old male with Type-2 diabetes	SGLT-2 inhibitors are a type of prescription medication (dapagliflozin)
3	Maruthappu *et al.*	*Med Clin North Am.* 2017	1	dapagliflozin	A 36-year-old woman with medication taking dapagliflozin	Ketoacidosis has been Diagnosed with elevated urinary ketone bodies
4	Wang *et al.*	*Diabetes Care* 2016	1	empagliflozin	A 40-year-old woman who had diabetic ketoacidosis with a high-anion gap following empagliflozin therapy	a severe high-anion gap was discovered
5	Redford *et al.*	*Kidney Med* 2020	1	10 mg dapagliflozin per day	A 58-year-old lady whose blood glucose level fell within 36 hours of the last dosage of insulin	advised to discontinue using insulin and solely take dapagliflozin

1.11 Conclusion of the Patient Case Studies

Based on the consideration and study of the above patient's cases, paying attention to the patient's diet and adverse effects when administering SGLT-2 inhibitors is crucial.

1.12 Some DKA treatment strategies include

Fluid therapy, insulin infusions via IV, and potassium and sodium bicarbonate delivery are all goals of DKA treatment.

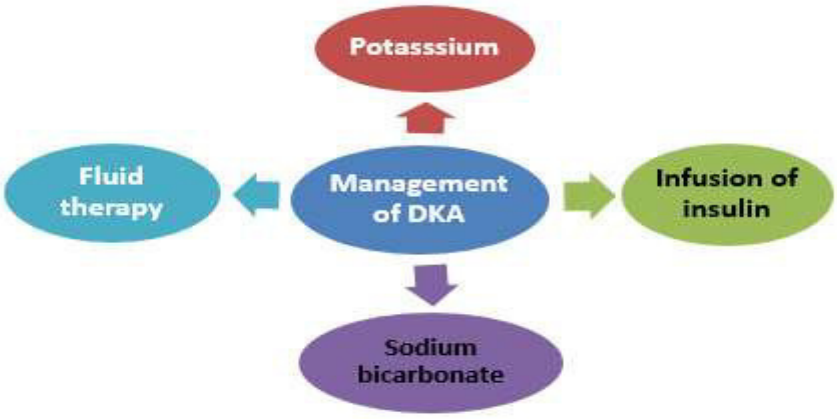

Fig-8:Management of Diabetes ketoacidosis[27,28]

These medicines should be stopped immediately if a patient is diagnosed with ketoacidosis. If DKA is detected early enough, it is easily reversible. Diabetes Ketoacidosis can be treated with IV fluid to alleviate dehydration caused by an insulin drip once it has been detected. To prevent hypoglycemia in a DKA patient, add 10-20% dextrose to the insulin drip. This treatment is used to restore the normal levels of sodium bicarbonate and anion gap. Patients with type-2 diabetes who are taking SGLT-2 inhibitors must stay hydrated and consume a sufficient amount of carbohydrates in their diet. In addition, potassium supplementation is necessary because SGLT-2 inhibitors deplete electrolytes such as potassium. Patients with metabolic acidosis also experience respiratory failure, necessitating tracheal intubation[27, 28] (Figure-8).

1.13 Fluid therapy

Fluid therapy is very significant in the treatment of dehydration. Isotonic saline (0.9 per cent NaCl) should be given at a rate of 500 to 1000 mL/h for the first 2 to 4 hours. After that, the rate of normal saline is reduced to 250 mL/h or 0.45 per cent saline, depending on the hydration condition. To allow sustained insulin administration and avoid hypoglycemia, the fluid comprises 5% dextrose with 0.45% NaCl at 150-250 mL/hr when the blood glucose level is corrected and reaches 200 mg/dl (11.1 mmol/l).

1.14 Potassium administration

Depletion of potassium occurs in metabolic acidosis and insulinopenia. Therefore, insulin is given at a rate of 10-20 mEq/hr to patients with a potassium level of 3.3 mEq/L until the potassium level exceeds 3.3 mEq/L.

1.15 Sodium Administration

According to clinical guidelines, sodium bicarbonate is not advised in patients with mild DKA and a pH greater than 7.0. However, in patients with DKA with a pH less than 6.9, the administration of 50 to 100 mmol sodium bicarbonate as an isotonic solution (in 400 ml of water) is advised. In the case of severe acidosis, bicarbonate therapy is not advised.

1.16 Insulin infusion

This is used to treat DKA because insulin has antilipolytic and antiketogenic properties, reducing ketone generation. 5% dextrose and insulin are used to keep glucose levels between 140 and 200 mg/dl. Some studies suggest that subcutaneous dosages of insulin analogues like Lispro and Aspart can be administered every 1-2 hours as an effective alternative to insulin infusions via IV[29].

1.17 Complications that occur while treating DKA

Hypoglycemia is a common complication that can occur during the treatment of diabetic ketoacidosis. Therefore, it's crucial to keep an eye on the insulin-treated patient, and dextrose should also be administered to avoid hypoglycemia. Another complication of DKA is hypokalaemia, which can be addressed by giving potassium to people with a serum potassium level of 3.3 mEq/L. Rhabdomyolysis is another complication of DKA, which can progress to kidney failure[29].

2. CONCLUSION

Complications such as ketoacidosis, a major side effect of sodium-glucose cotransporter-2 inhibitors, might occur in diabetic individuals who use them. Diabetic ketoacidosis is a possible side effect that has been recorded by the FDA and other emergency medical organizations following the use of SGLT-2 inhibitors in type-2 diabetes patients, as well as during off-label usage in type-1 diabetic patients. Therefore, the EMA and the FDA Adverse Event Reporting System do not suggest SGLT-2 inhibitors for patients with type-1 diabetes (FAERS). Aside from their negative side effects, this family of medicines has acquired appeal due to their glucose-lowering properties, as well as their ability to lower blood pressure (3-5 mmHg) and weight loss (1.5-3.5 kg)[30] Dapagliflozin, canagliflozin, and empagliflozin operate by inhibiting sodium-glucose cotransporter channels in PCT, decreasing glucose levels by preventing reabsorption, and limiting glucose availability in plasma[31]. This causes a lack of insulin and an increase in glucagon secretion, resulting in a metabolic shift toward free fatty acid breakdown (lipolysis) and ketoacidosis. A low carbohydrate diet, lowering insulin doses, stress, and surgery are all predisposing variables that worsen the situation of DKA[32]. The prevalence of DKA in COVID-19 patients has been connected to higher severity of death and length of stay in these patients, according to recent review studies published in 2021[33, 34]. The case of a patient who presented with COVID-19 symptoms and was later diagnosed with DKA is presented[35-37]. The increased prevalence of DKA during juvenile T1D diagnosis is concerning, highlighting the necessity of early screening programmes. Unlike a previous one in the United States, this study did not find a consistent, clinically relevant association between DKA at diagnosis and long-term HbA1c, raising concerns about the impact of other factors on long-term glycemic outcomes[38-40]. We briefly covered ketone body metabolism, different pathophysiologic pathways by which SGLT-2 inhibitors cause Diabetic ketoacidosis, the number of case reports involving SGLT-2 inhibitors-induced DKA, and what can be done to lessen this risk. SGLT-2 inhibitors-induced diabetic ketoacidosis can be avoided if signs and symptoms of DKA are recognized early[41, 42].

3. AUTHOR CONTRIBUTION STATEMENT

Ms Bhasin and Dr Mukesh Kumar Kumawat prepared the original draft of the review. Mr Manoj Kumar Sharma and Dr

Narender Yadav provided valuable inputs towards the design of the manuscript. All authors read and approved the final version of the manuscript.

4. CONFLICT OF INTEREST

Conflict of interest declared none.

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