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REVIEW

Predisposing factors for the development of diabetic ketoacidosis with lower than anticipated glucose levels in type 2 diabetes patients on SGLT2-inhibitors: a review

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Abstract

Purpose SGLT2-inhibitors (SGLT-2i) have been linked to the risk of potential life-threatening diabetic ketoacidosis (DKA). The U.S. Food and Drug Administration and the European Medicines Agency issued warnings in 2015 and 2016 respectively on the predisposing factors to the development of DKA in individuals on an SGLT2i. New predisposing factors to DKA are still being discovered with the use of SGLT-2i. The list by FDA and EMA is yet to be updated. This article aims to provide a holistic list that includes the newer factors that have been implicated in the development of DKA. The overall aim is to guide physicians in prescribing this class of drugs for type 2 diabetes mellitus (T2D).

Method A search was done using PUBMED, Google Scholar, and Directory of Open Access Journals with the following words: SGLT-2 Inhibitors AND Ketoacidosis were entered. We included articles from 2000 to 2020, those in English, those involving any of the approved SGLT2i medications in T2D patients, and studies that focused on DKA linked to SGLT-2i. These articles were reviewed, and relevant data extracted and compiled.

Results and conclusion The review has revealed that predisposing factors include (excess) alcohol consumption, female gender, starvation due to illness or fasting, withholding the use of SGLT2i for less than 48 h peri-operatively, and the existence of a variations in the expression of SGLT2 receptors. Patients should be advised on "sick day rules," and if a patient becomes unwell while on an SGLT2i, they should be advised to withhold the medication for the duration of the intercurrent illness.

Keywords Euglycemic diabetic ketoacidosis · SGLT2-inhibitors · Predisposing · Type 2 diabetes

Introduction

The incidence of type 2 diabetes mellitus (T2D) is steadily on the rise. T2D is no longer a disease for the adult population alone but is now seen, observed, and managed in children and adolescents [1]. Globally, the number of people with T2D has quadrupled in the past three decades and it is now the ninth major cause of death. The epidemic of T2D and its complications pose a major global health threat. The reasons for the escalating epidemic of diabetes mellitus are multiple, including population aging, economic development, urbanization, unhealthy eating habits, and sedentary lifestyles [2]. Over 90% of diabetes mellitus cases are type 2 diabetes mellitus [3–5]. Between 2010 and 2030, it has been predicted that there will be a 20% increase in the number of adults with diabetes mellitus in developed countries and a 69% increase in developing countries [6].

Medications used in the management of T2D include biguanides, sulfonylureas, meglitinides, thiazolidinediones, dipeptidyl peptidase (IV) Inhibitors, α-glucosidase inhibitors, GLP1-RA, and sodium-glucose cotransporter 2 inhibitors (SGLT-2i) [7]. The sodium-glucose cotransporter 2 inhibitors constitute a relatively new class of medications for the management of T2D [8, 9]. They are insulin-independent and act via enhancing glucose excretion by inhibiting the activity of sodium-glucose co-transporter-2 in the proximal tubule of the kidney. This is the renal mechanism for glucose and sodium

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reabsorption into the renal tubules, and inhibiting reabsorption leads to a reduction of blood glucose levels [10–12]. The use of this new class of agents has been associated with other non-glycemic effects including weight loss [13–15] and blood pressure reduction [16, 17] along with improving the outcome in heart failure and kidney disease [18, 19]. In addition, this class of medication has a low risk of causing hypoglycemia as their action is insulin-independent [20]. SGLT-2i have been linked to improved insulin sensitivity which also contributes to the improved glycemic control seen [21]. Since their approval, SGLT-2i have been associated with side effects such as genital infections [22], increased risk of fractures [16], euglycemic diabetic ketoacidosis (EuDKA) [16], and a mild increase in the levels of low-density lipoprotein [23, 24].

SGLT-2i medications' association with diabetic ketoacidosis (DKA) particularly euglycemic diabetic ketoacidosis has been the subject of considerable interest and concern. This is largely due to the presentation with normal or minimally elevated glucose levels making ketoacidosis more difficult to diagnose [25]. More so, the development of DKA being less common in T2D patients further increases the risk of underdiagnosis. The concern about the risk of EuDKA led the U.S. Food and Drug Administration and the European Medicines Agency to issue warnings in 2015 and 2016 respectively on the predisposing factors to the development of DKA in individuals on an SGLT2i [26, 27]. Being a relatively new class of drug, the knowledge base with respect to the usage of the drugs has continued to grow since their approval. This article aims to provide a review of the risk factors for diabetic ketoacidosis development in patients on SGLT-2i therapy particularly in relation to the warnings released by both the FDA and the EMA and their bearings on clinical practice (Fig. 1).

Illnesses

The role of illness in precipitating diabetic ketoacidosis is well established [28]. Conditions such as pneumonia [29], pancreatitis [30], poor food intake [31], abscesses [32], sepsis [33], and gastroparesis [34] have been linked to the development of EuDKA. Illness may decrease the consumption of carbohydrates which may lead to ketogenesis [31, 35]. In patients with type 2 diabetes on SGLT-2i, the reduction in carbohydrate intake plus the presence of low plasma glucose brought about by the glycosuria, suppresses insulin secretion leading to ketosis [36]. Ketosis is often followed by ketoacidosis with relatively normal or only slightly elevated blood glucose levels. Intercurrent illness often leads to insulin resistance. In the presence of relative insulinopenia, there is increased utilization of fatty acids leading to ketosis. This is more likely to happen in patients with type 1 diabetes. In type 2 diabetes, particularly in longer duration type 2 diabetes with reduced β-cell function [37], the glycosuric effect of SGLT2-2i makes ketogenesis more likely and the resulting ketosis contributes to EuDKA. The potential list of illnesses associated with EuDKA has continued to increase and now includes the following: toothache [31], pancreatitis secondary to hypertriglyceridemia [30], diffuse paralytic ileus, and urinary tract infections [38].

Insulin dose changes

Glycemic control is achieved in the human body through the balance between insulin levels and the level of counter-regulatory hormones such as glucagon, epinephrine, and glucocorticoid [39]. In the management of DKA, insulin plays a vital role reducing glycogenolysis, reducing gluconeogenesis, and also enhances glucose utilization by peripheral tissues and therefore impacts on the rate of ketogenesis [40]. Hyperglycemia is a direct consequence of the increase in gluconeogenesis and glycogenolysis brought about by insufficient insulin levels in diabetic patients. As the body is unable to utilize glucose in the absence of sufficient insulin, fatty acids are mobilized from adipose tissues by lipases. The breakdown products include ketones which may lead to ketoacidosis [39, 40]. Also, due to the relative insulin deficiency, elevated glucagon also stimulates ketogenesis through promotion of lipolysis in adipocytes and stimulation of beta oxidation of free fatty acids (FFAs) in the liver [41].

Peri-operative procedures

Surgery in patients on SGLT-2i has been the subject of much interest. Numerous cases where EuDKA developed in patients recovering from surgery have been reported [42–45]. A systematic review of twenty-five cases reported by Burke et al. [46] showed that approximately 30% of patients developed DKA while on SGLT-2i following surgery. The recommendations by the American College of Endocrinology as well as the American Association of Clinical Endocrinologists are that SGLT-2i should be withdrawn 24 h before surgery [47]. Hoffman et al. [43] and Chacko et al. [44] reported cases of DKA occurring even when SGLT-2i were withdrawn in accordance with the guidelines. In another report by Kameda et al., 2019 [47], a patient developed DKA following coronary artery by-pass graft surgery where the SGLT-2i had been withdrawn over 24 h before surgery. The average half-life of the common SGLT-2i used is between 10 and 13 h [15, 47, 48] which means that there could still be drug molecules exerting biological effects during the surgery. Chacko et al. [44] advised that SGLT-2i should be withheld for at least 48 h before surgery while Hoffman et al. [43] advised 72 h pre-surgery. Milder et al. [45] suggested withdrawing the SGLT2i

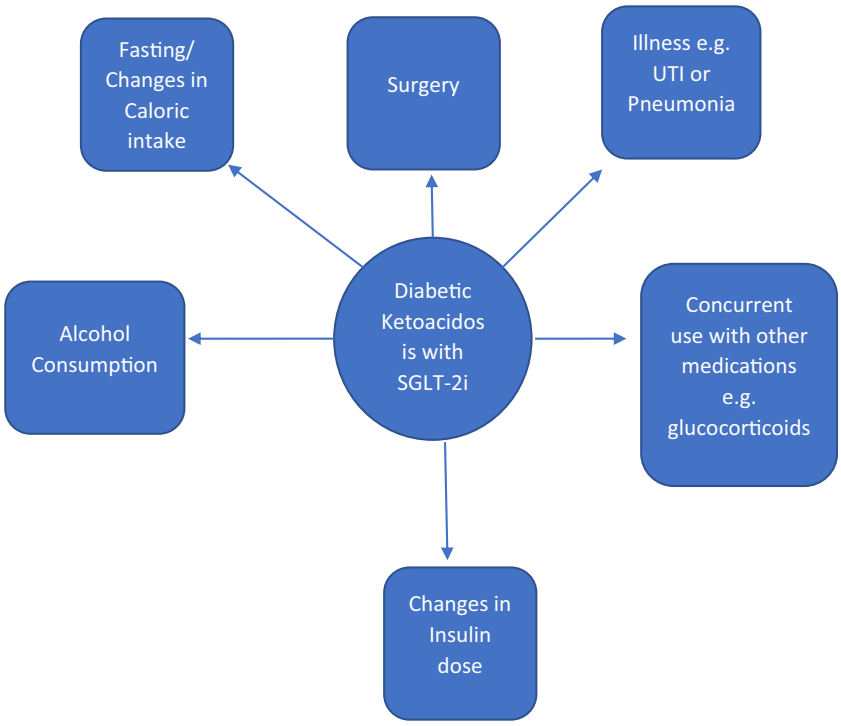

Fig. 1 Diagram showing the major conditions associated with euglycemic diabetic ketoacidosis with SGLT-2Inhibitors

48–72 h in advance of minor surgery. We agree with Hoffman et al. [43] and Chacko et al. [44] that local guidelines for safe perioperative procedures in patients on SGLT-2i therapy should be developed and these guidelines should be communicated appropriately.

Starvation, fasting, and low-carbohydrate diet

Changes in caloric intake especially decreased carbohydrate intake shift metabolism processes to the greater utilization of fat for energy. This alone can promote the production of ketone and thereby lead to DKA most especially under stressful conditions [49]. Low-carbohydrate diets as well as ketogenic diets such as the Atkins diet starve the body of glucose. Ketoses induce nausea, which can further reduce intake, and can then lead to ketoacidosis. These conditions favor the increase in counter-regulatory hormones plus increase the glucagon to insulin ratio in the presence of metabolic stress and insulin deficiency [49]. During times of decreased caloric intake, patients with diabetes who continue taking 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 normoglycemia [49–51]. In cases of prolonged fasting, near total glycogen depletion contributes to normoglycemia as metabolic acidosis continues to develop [52]. Furthermore, lipolysis and free fatty acid production are accelerated during fasting [52]. In addition, insulin is less effective at suppressing lipolysis and ketogenesis during a fast [52], thereby increasing the risk of developing ketoacidosis.

Gender

Females appear much more susceptible to EuDKA than men [32]. Limenta et al. [32] reported data on SGLT-2i-associated DKA from the Health Sciences Authority. The majority of reports were from women (75%). The cases reported were, however, categorized into diabetic ketosis, diabetic ketoacidosis, and EuDKA. The incidence of EuDKA in relation to gender was difficult to extract from this report. It is recognized, however, that the overall the rate of females treated for DKA far exceeds that of the males; this should be considered when prescribing SGLT2-i.

Alcohol consumption

Chronic alcohol consumption is associated with lipolysis as well as depleting body stores of carbohydrates and proteins [53]. Vomiting and starvation can result from excess alcohol consumption leading to dehydration [54]. When this occurs in a patient with diabetes on SGLT-2i, it can result in diabetic ketoacidosis. Long-term consumption of alcohol can also lead to liver damage increasing the risk for ketogenesis due to impairments in glycogenolysis. In some cases, starvation or alcoholic ketoacidosis (AKA) is an appropriate differential diagnosis. Measurement of the alcohol levels and observation

of whether insulin leads to improvements may be sufficient to exclude the latter [55]. Excluding the former may be challenging and often requires a good clinical history and serum bicarbonate measurements [56]. Clinicians should therefore be encouraged to explain the effects of alcohol consumption on patients taking SGLT-2i.

Non-alcoholic fatty liver disease is now recognized as a common cause of cirrhosis in type 2 diabetes [57]. It is suggested that SGLT2i, particularly empagliflozin [58], may reduce the risk of fatty liver disease. However, the use of SGLT2i in patients with established cirrhosis is less clear. One could predict problems with ketosis/DKA in diabetes patients on SGLT2i with reduced hepatic glycogen stores.

Genetics

The potential for a relatively unrecognized variant of the SGLT2 transporter has been proposed [59]. The authors suggested that the presence of the variant could lead to stronger binding of the SGLT-2i which could ultimately result in absolute, albeit transient, loss of insulin secretion. A recent study by Saponaro et al., 2020 [60] has shown that there is a variability in the expression of SGLT2 receptors and that this probably contributes to the variability of response for patients placed on SGLT-2i [61]. Further studies are required to investigate their variation among different populations and the extent to which these variants impact on the use of SGLT-2i in treatment [61]. The findings by Saponaro et al. hold much promise for future therapy with SGLT-2i, and they remain to be fully investigated.

Other factors

A number of other factors can contribute to the development of EuDKA in patients on SGLT-2i. Concurrent use of drugs might affect the counter-regulatory hormones and lead to alterations in serum glucose levels [62]. These include glucocorticoids [63], β-blockers [64], thiazide diuretics [65], atypical antipsychotics [66], protease inhibitors such as Ritonavir [67], and cocaine [56]. Cocaine has been linked to the development of DKA by virtue of its effect on counter-regulatory hormones [68].

There is also evidence that hepatic abnormalities that affect glycogen stores and ultimately impact on glycogenolysis may further exacerbate the relative insulinopenia eventually culminating in EuDKA [69, 70]. The contribution of hepatic abnormalities in the development of EuDKA in type 2 diabetes patients is still not clearly understood.

Conclusion

The use of SGLT2-i to treat T2D patients has continued to increase steadily over the past few years and, with this, the risk of developing SGLT2-i-associated DKA. Furthermore, due to the benefit shown in heart failure and renal dysfunction in both diabetes and non-diabetes individuals, the use of SGLT2-i is likely to increase further over the next few years.

Patients very rarely (if ever) develop SGLT2i-induced EuDKA or DKA when well. Certain precautions, however, do need to be kept in mind by clinicians to limit as much as possible, the occurrence of SGLT2-i-associated EuDKA. These include acute illness, patients undergoing perioperative procedures, patients that regularly consume alcohol, those deprived of calories (whether deliberately or not), and female patients. Patients with T2D who are unwell with ketones should be instructed to use "sick day rules." Advice given to patients on SGLT2-i should be similar to the advice given to patients on loop diuretics or ACEI/ARBs, and they should suspend their medication while unwell if possible. Clinicians should also consider the possibility of EuDKA in sick patients with T2D even with near-normal glucose levels. If there is a concern, urine should be checked for ketones and blood taken for plasma bicarbonate to inform the next clinical decisions.

Authors' contribution AOB came up with the idea for the study and wrote the first draft of the manuscript. IOO assisted with the literature search. IOO and AC made contributions to the writing and revision of the manuscript. AC critically revised the manuscript for intellectual content. All authors approved the final draft of the work.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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