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Navigating the Complexities of SGLT-2 Inhibitor Therapy: Balancing Benefits and Risks for Type 2 Diabetes Management

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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Letter to the Editor

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ABSTRACT

Sodium-glucose co-transporter 2 (SGLT-2) inhibitors have emerged as potent oral hypoglycemic drugs for managing type 2 diabetes, offering significant benefits such as improved cardiovascular and renal functions along with weight loss. However, their usage is accompanied by various risks, including urinary tract infections, vulvovaginal candidiasis, reduced bone mineral density, and the rare but serious condition known as euglycemic diabetic ketoacidosis (EDKA). Despite initial authorizations with perceived benefits outweighing risks, subsequent warnings by the FDA and recent studies have highlighted the elevated risk of diabetic ketoacidosis (DKA) associated with SGLT-2 inhibitors. This risk, particularly EDKA, presents diagnostic challenges due to attenuated hyperglycemia, potentially delaying accurate diagnosis and intervention. Furthermore, the lack of awareness and data in Asian regions underscores the importance of increased vigilance and research into the side effects of these drugs. Clinicians are advised to educate patients about

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potential adverse effects, consider discontinuation during certain conditions, and utilize advanced glucose meters for the early detection of DKA. This letter emphasizes the critical need for awareness, monitoring, and further investigation into the complexities surrounding SGLT-2 inhibitor therapy in type 2 diabetes management.

Keywords: SGLT-2 inhibitors; type 2 diabetes management; benefits; risks; diabetic ketoacidosis; Euglycemic Diabetic Ketoacidosis (EDKA).

Madam/Sir,

SGLT2 inhibitors are designed to primarily reduce glucose reabsorption in the renal system, leading to a significant decrease in blood glucose levels [1]. These agents serve as potent oral hypoglycemic drugs, often used after metformin therapy, providing notable benefits for cardiovascular and renal functions, and inducing weight loss [2]. Despite their effectiveness, SGLT-2 inhibitors come with drawbacks, including urinary tract infections, vulvovaginal candidiasis, reduced bone mineral density, and the rare but serious condition Euglycemic Diabetic Ketoacidosis (EDKA).

SGLT-2 inhibitors were authorized for diabetes treatment in 2012 with the understanding that their benefits outweighed risks. However, in May 2015, the FDA (Food and Drug Administration) issued warnings after documenting 20 cases of acidosis in SGLT2 inhibitor users, with a subsequent notice in December 2015 citing 73 cases
[3-4].

Another study, published on July 28, 2020, in the Annals of Internal Medicine, conducted an analysis of data spanning from 2013 to 2018 across seven Canadian provinces and the UK. Over 370,454 person-years, 521 patients were diagnosed with diabetic ketoacidosis (DKA), resulting in an incidence rate of 1.40 per 1000 person-years. Comparatively, SGLT-2 inhibitors, in contrast to DPP-4 inhibitors, demonstrated a higher risk of DKA, with an incidence rate of 2.03 versus 0.75. Specific hazard ratios were 1.86 for dapagliflozin, 2.52 for empagliflozin, and 3.58 for canagliflozin. Notably, neither age nor sex influenced this association, and a perceived reduction in risk was observed with prior insulin use [5].

In a separate study in 2017, published in Diabetes/Metabolism Research and Reviews, an examination of the FDA's adverse reporting system revealed a sevenfold increased likelihood of diabetic ketoacidosis associated with SGLT-2 inhibitors. Notably, approximately two-thirds of reported DKA cases met the criteria for Euglycemic Diabetic Ketoacidosis (EDKA) [6].

However, South-East Asia, with almost 90.2 million people with diabetes [7], lacks data and awareness regarding these effects. Given the absence of conspicuous elevation in blood glucose levels, a characteristic feature of diabetic ketoacidosis (DKA), clinicians confront a diagnostic quandary in the case of euglycemic diabetic ketoacidosis (EDKA). The attenuated hyperglycemia, lower than what is typically anticipated, introduces complexity into the clinical scenario, potentially protracting the interval between symptom onset and accurate diagnosis [8]. Such delays in identification and subsequent intervention can contribute to exacerbated outcomes for individuals grappling with EDKA. Clinicians and patients must be aware of these complications. More studies should be done on side-effects of these drugs. Physicians initiating SGLT-2 inhibitor therapy are advised to thoroughly counsel patients on potential adverse effects, particularly those rare in occurrence. Discontinuation of SGLT-2 inhibitors is imperative during instances of infection, dehydration, surgical interventions, prolonged vomiting, or diarrhea, with immediate medical consultation sought. Additionally, offering patients a glucose meter equipped with advanced capabilities for blood ketone monitoring represents a prudent strategy, serving as an early detection mechanism for diabetic ketoacidosis (DKA) in individuals deemed to be at heightened risk.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

We hereby declare that we have not utilized any AI technology during the process of writing or editing the manuscript.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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