Diabetes Research: Open Access

Commentary

DOI: https://doi.org/10.36502/2025/droa.6191

Expanding Applications of Sodium-Glucose Cotransporter-2 Inhibitors (SGLT-2i) with Attention to Euglycemic Ketoacidosis (Eka) for No Diabetic History

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Received date: 26 March 2025; **Accepted date**: 17 April 2025; **Published date**: 23 April 2025

Citation: Bando H, Wood M, Ebe K. Expanding Applications of Sodium-Glucose Cotransporter-2 Inhibitors (SGLT-2i) with Attention to Euglycemic Ketoacidosis (Eka) for No Diabetic History. Diab Res Open Access. 2025 Apr 23;6(1):06-10.

Abstract

Sodium-glucose cotransporter-2 inhibitors (SGLT-2i) have their origins in phlorizin, which was discovered in apple bark in 1835. SGLT-2i has been effective in treating type 2 diabetes (T2D), chronic kidney disease (CKD), and cardiovascular disease (CVD). In heart failure, cardiac tissue becomes less able to metabolize glucose and fatty acids, and begins to rely more on ketone bodies. Subjects with heart failure with reduced ejection fraction showed higher cardiac output at rest and lower filling pressures, cardiac volumes, and NT-proBNP levels when treated with ketone esters. As an adverse effect of SGLT-2i, euglycemic ketoacidosis (eKA) has been reported and requires careful attention.

Keywords

Sodium-Glucose Cotransporter-2 Inhibitors, Phlorizin, Ketone Bodies, Euglycemic Ketoacidosis, STICH Protocol, Euglycemic Diabetic Ketoacidosis

Abbreviations

SGLT-2i: Sodium-Glucose Cotransporter-2 Inhibitors; eKA: Euglycemic Ketoacidosis; eDKA: Euglycemic Diabetic Ketoacidosis

Commentary

From a historical point of view, the development of sodium-glucose cotransporter-2 inhibitors (SGLT-2i) began with phlorizin, which was discovered in apple bark in 1835 [1]. In 1933, it was reported that phlorizin promotes glucose excretion in the urine, but its oral administration was hindered by poor stability. Subsequently, SGLT-2 inhibitors with improved selectivity and stability were developed through chemical modification.

SGLT-2i were initially approved for blood glucose control in patients with type 2 diabetes (T2D). However, their effectiveness in treating chronic kidney disease

(CKD) and cardiovascular disease (CVD) has since been demonstrated, leading to an expansion of their indications [2]. Dapagliflozin, one such SGLT-2i, suppresses CKD progression. In Japan, it is estimated to increase predicted life expectancy by 0.84 years—a significant improvement. The medical market for SGLT-2i is growing rapidly, driven primarily by their expanded use in CKD and heart failure.

When administered orally, SGLT-2i are filtered by the kidneys and bind to SGLT-2 receptors, thereby inhibiting glucose reabsorption. This promotes urinary glucose excretion and lowers blood glucose levels. Although the cardioprotective effects of SGLT-2i are not yet fully understood, they appear to be independent of glucose-lowering action. Proposed mechanisms include regulation of ion exchange in cardiomyocytes, suppression of the sympathetic nervous system, natriuretic effects, blood pressure reduction, improvement in ventricular remodeling, and reduction of oxidative stress [3,4]. The increased availability of ketone bodies in conditions such as heart failure may contribute to these benefits [5]. Under normal conditions, fatty acid oxidation provides 50–70% of the heart's energy [6]. In heart failure, cardiac tissue becomes less capable of metabolizing glucose and fatty acids and begins to rely more on ketone bodies [7]. Interestingly, patients with heart failure with reduced ejection fraction had higher resting cardiac output and lower filling pressures, cardiac volumes, and NT-proBNP levels when treated with ketone esters compared to isocaloric controls [8] (**Fig-1**).

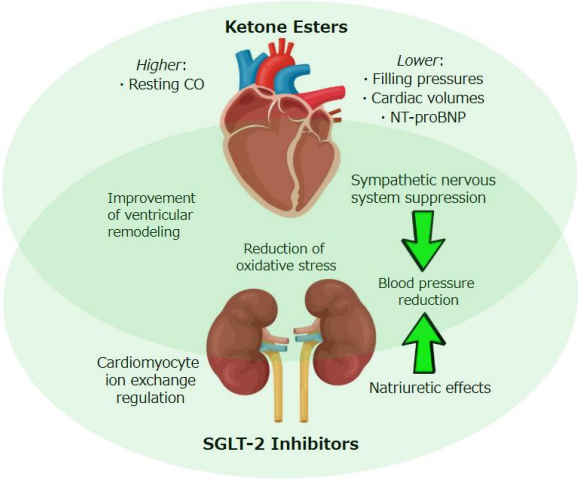

Fig-1: Overlap of the Cardioprotective Effects of Ketone Esters and SGLT-2 Inhibitors

As an adverse effect of SGLT-2i, euglycemic ketoacidosis (eKA) has been reported [9]. Despite normal blood glucose levels, ketoacidosis can develop and may be easily overlooked. Furthermore, ketoacidosis can progress even without hyperglycemia if insulin is discontinued. In recent years, life-threatening eKA has been reported in non-diabetic patients taking SGLT-2i for heart failure and CKD treatment [10].

Three major studies have reported the occurrence of euglycemic diabetic ketoacidosis (eDKA). In the EMPA-REG OUTCOME trial, which targeted T2D patients, the addition of empagliflozin to standard treatment reduced cardiovascular events and mortality. The incidence of eDKA was similar between the empagliflozin and placebo groups. In the DECLARE-TIMI 58 trial, which targeted T2D patients at risk for atherosclerosis, dapagliflozin reduced cardiovascular death and hospitalization due to heart failure, although the incidence of eDKA was higher in the dapagliflozin group than in the placebo group. In the DAPA-HF trial, dapagliflozin reduced the risk of worsening heart failure and cardiovascular death in patients with heart failure and reduced ejection fraction, regardless of whether they had T2D. eDKA is rare and occurs only in diabetic patients.

Recent reports have shown that eDKA is a rare metabolic disturbance observed in both type 1 and type 2 diabetes [11]. Although uncommon, it is a life-threatening adverse effect of SGLT-2i, which are otherwise known for their antidiabetic, renal, and cardiovascular benefits [12]. A recent study investigated 51 patients diagnosed with eDKA [13]. Of these, 19 were treated with SGLT-2i and 32 were not. Patients using SGLT-2i were significantly older than non-users ($p < 0.001$). SGLT-2i users also had higher rates of urinary tract infections (UTI), genitourinary infections, and vulvovaginitis. Plasma blood glucose (PBG) levels were significantly higher in non-users than in users. These findings suggest that SGLT-2i may significantly influence the occurrence of genitourinary infections in patients with DKA.

In daily clinical practice within diabetes and primary care settings, healthcare providers consistently consider the possibility of DKA in patients taking SGLT-2i. In

particular, it is essential to conduct thorough medication reviews for both inpatients and outpatients, checking for chronic pancreatitis, acute illness, sufficient oral intake, or other risk factors associated with SGLT-2i. A recent report highlighted key risk factors for DKA associated with SGLT-2i, including major acute illnesses, reduced oral intake, dehydration, chronic pancreatitis, and a history of DKA [14]. During our routine clinical practice, medical staff remain vigilant for DKA symptoms in patients taking SGLT-2i and conduct complete medication reconciliation for admitted and outpatient clinic patients.

The usefulness of SGLT-2i is widely recognized across various clinical settings, including diabetes outpatient clinics, general wards, and intensive care units. Although there have been few reported cases of eDKA [15], the actual incidence is believed to be higher than commonly perceived [16]. Studies have shown that the use of SGLT-2i doubles the risk of eDKA compared to glucagon-like peptide-1 receptor agonists (GLP-1Ra) and triples it compared to DPP-4 inhibitors [11,12]. A large-scale network meta-analysis involving 138,322 subjects from 36 randomized controlled trials (RCTs) demonstrated that SGLT-2i significantly increase the risk of DKA, with an odds ratio of 2.07, supported by strong evidence [17]. As prescriptions for SGLT-2i continue to rise, eKA—characterized by metabolic acidosis in the presence of normal or mildly elevated glucose levels—may become increasingly common and overlooked. Therefore, clinicians must remain aware of this possibility during all phases of care.

The British Diabetes Society has outlined essential guidelines for inpatient care [18]. A new section was added to address the rising concern of eKA associated with SGLT-2i. Treatment follows the STICH protocol:
i) Stop SGLT-2i,
ii) Insulin at 0.1 units/kg/hour,
iii) Carbohydrates to maintain blood glucose, and
iv) Hydration with sufficient fluids.

In summary, SGLT-2i have shown benefits including improving heart failure outcomes, reducing cardiovascular mortality, and slowing CKD progression [19]. Accordingly, SGLT-2i have received a Class 1A recommendation for the treatment of T2D, CKD, and heart failure—regardless of ejection fraction [20]. However, eKA is a life-threatening emergency [21]. As described above, appropriate attention to eKA in clinical practice is essential, and this article may serve as a valuable reference.

Conflict of Interest

The authors have read and approved the final version of the manuscript. The authors have no conflicts of interest to declare.

Funding

There was no funding received for this paper.

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