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ADVERSE EFFECTS OF SGLT2 INHIBITORS - A LITERATURE REVIEW

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ABSTRACT

Introduction: Sodium-glucose cotransporter-2 (SGLT2) inhibitors have rapidly become foundational in the management of type 2 diabetes mellitus (T2DM), chronic kidney disease (CKD), and heart failure (HF), offering robust glycemic control and cardioprotective and renoprotective benefits. However, despite their favorable efficacy profile, clinicians must recognize and monitor for known adverse events associated with this drug class.

Aim of the study: The aim of this study was to systematically analyze and synthesize current evidence regarding the adverse effects associated with sodium–glucose cotransporter 2 (SGLT2) inhibitors. Particular emphasis was placed on identifying the most frequently reported complications, evaluating their underlying mechanisms, and assessing their clinical relevance in various patient populations. The study also sought to determine potential risk factors predisposing patients to these adverse outcomes and to discuss implications for clinical practice.

Material and methods: This study was designed as a review of the available literature. A structured search of biomedical databases was undertaken to identify peer-reviewed publications addressing adverse effects associated with SGLT2 inhibitors. Eligible sources included original research articles, randomized controlled trials, meta-analyses, and systematic reviews. Studies were selected according to their relevance and scientific rigor. Extracted data focused on the frequency, mechanisms, and clinical implications of reported adverse events. The collected evidence was synthesized descriptively to present a comprehensive overview of the safety profile of this therapeutic class.

Results and Conclusions: Common complications include genitourinary infections, especially genital mycotic infections, which are consistently reported across studies, and urinary tract infections, though the latter's magnitude of risk may vary by agent and population subgroup. Meta-analyses suggest increased risks of diabetic ketoacidosis, particularly in its euglycemic form, and osmotic diuresis-related events such as volume depletion and hypotension. Serious but rare events identified in pharmacovigilance data include limb amputations. While SGLT2 inhibitors may not significantly elevate overall serious adverse event incidence in controlled settings, the risk profile requires careful patient selection and monitoring. SGLT2 inhibitors retain an overall favorable benefit–risk balance when used appropriately. Nevertheless, clinicians should maintain vigilance for specific complications—especially genitourinary infections and metabolic disturbances—and tailor therapy with risk stratification and preventive strategies. Continued surveillance and research are warranted to optimize long-term safety.

KEYWORDS

SGLT2 Inhibitors, Adverse Effects, Diabetic Ketoacidosis, Genitourinary Infections, Hypotension, Type 2 Diabetes Mellitus

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Introduction

Sodium–glucose cotransporter-2 (SGLT2) inhibitors are a class of glucose-lowering agents originally developed for the treatment of type 2 diabetes mellitus (T2DM). Over the past decade, large randomized controlled trials and systematic reviews have expanded their clinical application beyond glycemic control to include prevention of heart failure (HF) hospitalization and slowing progression of chronic kidney disease (CKD), irrespective of baseline diabetes status [1,2]. While they are generally considered well tolerated with an overall favorable safety profile, an increasing body of evidence has elucidated a distinct spectrum of adverse events that can complicate their use in routine practice [3]. Mechanistically, SGLT2 inhibition increases renal glucose excretion, leading to glucosuria and osmotic diuresis. Although this underlies many of the therapeutic benefits, it also creates a biological milieu conducive to genitourinary complications. The most consistently reported adverse effects are genital mycotic infections, particularly candidiasis, with a significantly elevated risk compared with control therapies in both clinical trials and observational cohorts [4]. The effect on urinary tract infections (UTIs) appears more nuanced, with some studies showing increased incidence while others report minimal association after adjustment for patient factors such as glycemic control and duration of diabetes [5,6]. Metabolic complications are another recognized class of SGLT2 inhibitor–associated events. Diabetic ketoacidosis (DKA), including euglycemic presentations characterized by only modest hyperglycemia, has been documented in multiple systematic reviews and meta-analyses, highlighting the need for heightened clinical vigilance, particularly in susceptible populations such as those with insulin deficiency or acute illness [7,8]. Although rare, these episodes can be severe and carry substantial morbidity [7]. Beyond the more common genitourinary and metabolic events, pharmacovigilance data have identified rare but serious complications such as lower-limb amputations [9]. Real-world safety analyses suggest that advanced age and comorbid conditions modulate both the frequency and severity of SGLT2 inhibitor–associated adverse events, reinforcing the need for individualized risk assessment [10].

A comprehensive understanding of these complications is essential for clinicians to balance the substantial cardiometabolic and renoprotective benefits of SGLT2 inhibitors with their risk profile. This is particularly crucial as indications expand to populations without diabetes and as use increases worldwide.

Mechanism of action

Sodium–glucose cotransporter-2 (SGLT2) inhibitors were initially developed as antihyperglycemic agents for patients with type 2 diabetes mellitus by targeting the SGLT2 protein in the renal proximal tubule to reduce glucose reabsorption and promote glucosuria, thereby lowering plasma glucose and HbA1c levels [11,12]. However, landmark clinical trials and updated guideline recommendations have substantially expanded their therapeutic indications beyond glycemic control. SGLT2 inhibitors are now recommended for the reduction of heart failure-related hospitalization and cardiovascular death in patients with heart failure with reduced or preserved ejection fraction, irrespective of the presence of diabetes, based on consistent evidence of cardioprotective benefits [13,14]. In addition, these agents are indicated for slowing the progression of chronic kidney disease and reducing the risk of sustained decline in estimated glomerular filtration rate (eGFR) in patients with chronic kidney disease, both with and without type 2 diabetes mellitus [15,16]. The underlying mechanisms extend well beyond glucose lowering and involve modulation of renal hemodynamics, natriuresis, and systemic volume status; restoration of tubuloglomerular feedback reduces intraglomerular pressure and attenuates hyperfiltration, contributing to nephroprotection [12]. SGLT2 inhibition also induces mild osmotic diuresis and natriuresis, which lower preload and afterload and improve cardiovascular load conditions [14,17]. Additionally, metabolic effects such as improved insulin sensitivity, enhanced ketogenesis favoring efficient myocardial energy utilization, and reductions in serum urate and oxidative stress have been implicated in their pleiotropic benefits [12,18]. At the cellular level, SGLT2 inhibitors may reduce tubular glucotoxicity and renal oxygen demand, ameliorate inflammation, and modulate neurohormonal pathways, collectively contributing to their cardiometabolic and renoprotective profile [12,19]. Consequently, current clinical use of SGLT2 inhibitors encompasses type 2 diabetes mellitus management, heart failure treatment, and chronic kidney disease progression mitigation, reflecting a paradigm shift toward organ-protective therapy grounded in multifaceted mechanisms of action [13,14,15,16].

Genitourinary Infections

Genitourinary infections represent the most frequently reported adverse event associated with the use of sodium–glucose cotransporter 2 (SGLT2) inhibitors [20,21,22,23]. The increased risk of these infections is directly related to the pharmacological mechanism of this drug class, which involves inhibition of renal tubular glucose reabsorption, leading to persistent glucosuria. The presence of glucose in the urine promotes microbial colonization and proliferation within the genital area and urinary tract [21,22]. Meta-analyses of randomized controlled trials have demonstrated that the increased risk predominantly concerns fungal infections, particularly those caused by Candida species. These infections were generally mild to moderate in severity and rarely led to permanent discontinuation of therapy. Randomized clinical trials and meta-analyses have consistently demonstrated a significantly increased risk of genital infections in patients treated with SGLT2 inhibitors compared with placebo and other antihyperglycemic agents. The increase mainly concerns infections of fungal etiology, whereas the effect of SGLT2 inhibitors on the incidence of classical bacterial urinary tract infections (UTIs) remains less conclusive. In clinical trials involving dapagliflozin, a higher incidence of events suggestive of genitourinary infections was observed; however, data regarding confirmed urinary tract infections were not consistent across analyses. In the EMPA-REG OUTCOME trial, no clinically significant increase in the risk of urinary tract infections was observed in patients receiving empagliflozin compared with placebo, despite a higher incidence of genital infections [21]. Observational studies provide additional insight into infection risk in routine clinical practice. In a population-based cohort study conducted in Japan, the use of SGLT2 inhibitors was associated with a reduced risk of bacterial urinary tract infections and, simultaneously, with an increased risk of bacterial genital infections [25]. Similar findings were reported in studies conducted in Korea, where the incidence of genital infections was higher in patients treated with SGLT2 inhibitors compared with other add-on therapies combined with metformin [23]. Multiple analyses have also confirmed a significantly increased risk of fungal genital infections in patients receiving SGLT2 inhibitors compared with control groups [21,23,24,25]. Furthermore, comparative studies have shown that the risk of fungal urinary tract infections, including those caused by Candida species, is higher in patients treated with SGLT2 inhibitors than in those receiving GLP-1 receptor agonists [22]. These differences are clinically relevant when selecting therapy in patients with a history of recurrent fungal infections and highlight the importance of individualized treatment decisions based on patient risk profile. Data from cohort studies conducted in the United States indicate that the risk of genital infections during the first 12 months after initiation of SGLT2 inhibitor therapy is significantly higher compared with treatment using DPP-4 inhibitors. Similar observations were made among patients with type 2 diabetes treated with metformin in combination with SGLT2 inhibitors, in whom the incidence of genital infections was higher than in those receiving metformin combined with DPP-4 inhibitors [23]. Nevertheless, the absolute risk increase remained moderate, and the majority of infections were uncomplicated. These findings confirm consistency between randomized clinical trials and real-world population analyses.

Hypotension

SGLT2 inhibitors, by inhibiting sodium and glucose reabsorption in the proximal renal tubule, induce glucosuria, natriuresis, and osmotic diuresis, leading to a reduction in intravascular volume and a decrease in blood pressure [26,29]. This mechanism contributes to the beneficial hemodynamic effects observed with this drug class but may also increase the risk of volume depletion, particularly in patients with predisposing factors [29]. A meta-analysis of randomized controlled trials including more than 68,000 patients demonstrated a significantly increased risk of volume depletion-related events in individuals treated with SGLT2 inhibitors compared with control groups [26]. The risk was particularly evident in patients with reduced glomerular filtration rate and in those receiving concomitant diuretics or other antihypertensive agents [26,29]. However, the absolute incidence of such events remained low. The highest risk was observed in populations with high cardiovascular and renal risk. Observational data indicate that the risk of severe hypovolemia is greatest during the initial phase of SGLT2 inhibitor therapy. Analyses have shown that the highest risk occurs within the first 30 days after treatment initiation, with a peak between the second and fourth week of therapy [28]. The clinical presentation of hypovolemia includes dizziness, weakness, hypotension, and laboratory indicators of dehydration [29]. This observation has important practical implications and supports closer monitoring during the first month of therapy. The mechanism is related to dynamic changes in sodium and water balance following treatment initiation. Orthostatic hypotension, as a potential consequence of reduced circulating blood volume, has been evaluated separately. A meta-analysis of randomized controlled trials did not demonstrate a statistically significant increase in the risk of orthostatic hypotension in patients treated with SGLT2 inhibitors

compared with placebo or other antihyperglycemic agents [27]. These findings suggest that despite the biologically plausible blood pressure-lowering mechanism, clinically overt orthostatic hypotension is not a frequent complication of SGLT2 inhibitor therapy. Nevertheless, caution is warranted in patients with low baseline blood pressure, autonomic dysfunction, chronic kidney disease, or conditions associated with increased fluid loss, such as diarrhea or fever [29,30]. Monitoring of blood pressure, body weight, and symptoms of dehydration is recommended after therapy initiation, and adjustment of concomitant treatment should be considered when appropriate [29]. In summary, SGLT2 inhibitors are associated with a moderate increase in the risk of hypovolemia, particularly during the early phase of treatment, whereas current evidence does not confirm a clinically significant increase in the incidence of orthostatic hypotension. Appropriate patient selection and monitoring of hemodynamic parameters allow for safe use of this drug class in clinical practice.

Hypoglycemia

Hypoglycemia is one of the most serious complications of pharmacological treatment of diabetes and significantly affects prognosis and quality of life. However, SGLT2 inhibitors demonstrate a favorable safety profile in this regard, which is directly related to their insulin-independent mechanism of action. Available data from clinical trials and observational analyses indicate that the use of SGLT2 inhibitors as monotherapy or in combination with agents with low hypoglycemic potential is not associated with a significant increase in the risk of hypoglycemic episodes compared with placebo or other modern glucose-lowering therapies [31,32]. Large population-based studies conducted among patients with type 2 diabetes, including those with chronic kidney disease, have shown that SGLT2 inhibitors are associated with a significantly lower risk of hypoglycemia requiring medical intervention compared with sulfonylureas, highlighting their metabolic safety advantage over older classes of glucose-lowering agents [33]. These findings are consistent with safety analyses from randomized clinical trials, in which the incidence of hypoglycemia during SGLT2 inhibitor therapy was low and comparable to placebo [32,34]. It should be emphasized, however, that the risk of hypoglycemia may increase when SGLT2 inhibitors are used in combination with insulin or insulin secretagogues. Systematic reviews and current clinical guidelines recommend dose reduction of agents with high hypoglycemic potential and close glycemic monitoring in such situations, particularly in elderly patients and those with impaired renal function [31,35]. In conclusion, current evidence indicates that SGLT2 inhibitors are characterized by a low risk of hypoglycemia, which constitutes one of their major clinical advantages; however, maintaining this safety profile requires appropriate individualization of combination therapy.

Diabetic ketoacidosis

Recent evidence indicates that therapy with sodium–glucose cotransporter-2 (SGLT2) inhibitors is associated with an increased risk of diabetic ketoacidosis (DKA) in patients with diabetes. A 2022 systematic review and meta-analysis of seven randomized controlled trials (42,375 participants) and five observational studies (318,636 participants) reported absolute DKA incidences of 0.6–2.2 per 1,000 person-years in RCTs and 0.6–4.9 per 1,000 person-years in observational cohorts. Relative risk estimates indicated a 2.46-fold increase in RCTs (RR 2.46; 95% CI 1.16–5.21) and a 1.74-fold increase in observational studies (RR 1.74; 95% CI 1.07–2.83) compared with control therapies [8]. A network meta-analysis of 73 studies (85,997 participants) confirmed higher odds of DKA with SGLT2 inhibitors (OR 1.83; 95% CI 1.35–2.46), with individual agents, including dapagliflozin, canagliflozin, sotagliflozin, and ertugliflozin, showing broadly similar risk profiles, suggesting a class-wide effect. Risk was elevated across both lower- and higher-dose regimens. Overall, although the absolute incidence of DKA remains low, SGLT2 inhibitor therapy confers a modest but clinically meaningful increase in risk, emphasizing the importance of careful patient selection, monitoring, and risk mitigation in high-risk populations [36]. Diabetic ketoacidosis (DKA) is a severe metabolic complication typically characterized by hyperglycemia, acidosis, and elevated ketone levels, most common in type 1 diabetes but also occurring in type 2 diabetes under metabolic stress [7]. Patients present with nonspecific clinical symptoms, including nausea, vomiting, abdominal pain, dyspnea, and general malaise [37,38]. Sodium–glucose cotransporter-2 inhibitors (SGLT2i) can alter its presentation, often producing euglycemic DKA with only modest hyperglycemia (blood glucose <250-300 mg/dL), lower HbA1c, and minimal changes in serum sodium, which may delay diagnosis [7,37,38]. Biochemically, euDKA is characterized by high anion gap metabolic acidosis with reduced serum bicarbonate and arterial pH, accompanied by elevated circulating ketone bodies, particularly β-hydroxybutyrate [37]. The risk of euglycemic DKA is markedly increased in SGLT2i users (OR 22.4; 95% CI 7.44–67.47), yet short-term

outcomes—including hospital stay, intensive care admission, and in-hospital mortality—are comparable to conventional DKA. The distinct clinical phenotype of SGLT2 inhibitor-associated DKA emphasizes the importance of clinician awareness of its euglycemic presentation, which may delay diagnosis if blood glucose alone is monitored [7]. Early recognition and management guided by ketone measurements and acid-base assessment are essential to avoid misdiagnosis and mitigate morbidity [7,38]. Euglycemic DKA may progress to severe systemic metabolic derangements if unrecognized promptly, due to its non-specific symptomatology and subtle biochemical features compared with classical hyperglycemic DKA. The mechanisms by which SGLT2 inhibitors contribute to the development of diabetic ketoacidosis are multifactorial. By lowering circulating glucose levels, these agents can induce a relative insulin deficiency, thereby stimulating lipolysis and hepatic ketone production. Additionally, the preferential reduction of insulin relative to glucagon enhances ketogenesis, further promoting the accumulation of ketone bodies [38]. Concomitantly, increased urinary glucose excretion can mask hyperglycemia, resulting in only modest elevations in blood glucose despite significant ketonemia, which may delay recognition and diagnosis of DKA [38,39]. Multiple clinical factors increase the likelihood of SGLT2 inhibitor-associated ketoacidosis. Younger age (<45 years), concomitant insulin therapy, and certain oral antihyperglycemic agents (e.g., acarbose) were identified as independent risk factors in retrospective analyses [40]. Intercurrent illness, surgery, reduced oral intake, dehydration, and metabolic stress are common precipitating factors in patients developing ketoacidosis while on SGLT2 inhibitors [7,41]. Impaired pancreatic β-cell function and longer diabetes duration also contribute to risk, particularly when endogenous insulin reserves are limited [42].

Limb amputation and fracture

Concerns have arisen regarding the risk of limb amputation and fractures associated with the use of sodium–glucose cotransporter-2 (SGLT2) inhibitors. Emerging evidence suggests a small but statistically significant increased risk of lower limb amputation (LA) associated with SGLT2 inhibitor use across a broad range of randomized controlled trials. A comprehensive network meta-analysis of 90 articles (including 96,522 participants for LA outcomes) reported an increased odds ratio (OR) for amputations of approximately 1.2 (95% CI: 1.1–1.3) among patients treated with SGLT2 inhibitors versus controls. Among individual agents, canagliflozin was specifically associated with a higher risk of lower limb amputation (OR 1.6; 95% CI: 1.1–2.4), whereas data regarding other SGLT2 inhibitors remain less consistent. Canagliflozin was associated with an approximately two-fold higher rate of lower limb amputations — predominantly at the toe or metatarsal level — compared with placebo in type 2 diabetes patients at high cardiovascular risk within the CANVAS Program [44]. Subgroup analyses identify patient characteristics linked to increased LA risk, including age between 40–65 years, obesity (BMI >30 kg/m²), elevated glycated hemoglobin (HbA1c >7%), and longer duration of diabetes (>10 years), highlighting populations that may require heightened clinical vigilance [43]. However, updated meta-analyses focusing on randomized data have also observed no statistically significant increase in amputation risk overall, particularly in shorter-term studies or when excluding long duration follow-up data, illustrating ongoing uncertainty in the magnitude of risk across different clinical settings [45]. Additional observational research comparing SGLT2 inhibitors with incretin-based therapies has not consistently demonstrated a higher risk of lower limb amputation among SGLT2i users, suggesting potential confounding effects related to comparator choice and residual patients ’baseline vascular risk [46]. Several hypotheses have been proposed to explain why SGLT2 inhibitors could be associated with lower limb and skeletal adverse events. Osmotic diuresis leading to volume contraction may theoretically compromise peripheral perfusion, particularly in patients with pre-existing peripheral artery disease, thus increasing susceptibility to foot ulceration and subsequent amputation [47]. In contrast, comprehensive analyses of fracture outcomes suggest that SGLT2i use does not confer a significant increase in overall fracture risk, and some population-based cohort data even indicate a reduced incidence of hip fractures relative to other glucose-lowering therapies [48,49].

Acute kidney injury

Current clinical data from large-scale studies indicate that acute kidney injury (AKI) incidence does not rise with SGLT2 inhibitor use and may be lower in patients treated with these agents compared with placebo or other glucose-lowering medications [50]. The aggregated evidence from cohort meta-analyses suggests that SGLT2 inhibitors contribute to a notable reduction in the likelihood of acute kidney injury relative to non-SGLT2 therapeutic strategies in broad clinical populations, including patients with conditions such as type 2 diabetes, heart failure, and chronic kidney disease [51]. Renal responses to SGLT2 inhibitors involve a complex coordination of both vascular and cellular processes [52]. By reducing proximal tubular glucose and sodium reabsorption, these agents increase distal sodium delivery and augment tubuloglomerular feedback, leading to afferent vasoconstriction and decreased intraglomerular pressure. This physiological adjustment mitigates glomerular hyperfiltration and lowers metabolic stress on tubular cells — effects that are hypothesized to reduce susceptibility to ischemic or toxic injury [52,53]. Preclinical evidence indicates that SGLT2 inhibitors support kidney health through mechanisms such as improved oxygenation, suppression of oxidative stress, and regulation of inflammation, which may collectively delay or prevent the onset of acute kidney injury [54]. Nonetheless, the temporary reduction in eGFR observed shortly after starting SGLT2 therapy is a well-documented hemodynamic effect that requires careful clinical assessment [55]. Although generally safe for renal outcomes, SGLT2 inhibitors may pose a higher risk of acute kidney injury in certain patients, highlighting the need for careful monitoring. Factors identified in retrospective cohorts include older age, impaired baseline eGFR, increased serum creatinine, albuminuria, and coexisting conditions such as dehydration or electrolyte disturbances, all contributing to greater AKI susceptibility. [56,57]. Taken together, the evidence underscores the kidney-protective effects of SGLT2 inhibitors, yet identifies circumstances in which heightened renal surveillance may be warranted [50].

Conclusions

Sodium–glucose cotransporter-2 (SGLT2) inhibitors continue to provide substantial improvements in cardiovascular and renal outcomes for patients with type 2 diabetes mellitus, heart failure and chronic kidney disease, reinforcing their broad clinical utility. However, their use is accompanied by a distinct spectrum of adverse events that clinicians must monitor closely. Genitourinary infections—particularly genital mycotic infections—are among the most frequently observed complications and occur at significantly higher rates compared with other glucose-lowering therapies [58,59,60]. Diabetic ketoacidosis (especially its euglycemic variant) has been documented in clinical settings and meta-analyses, underscoring the need for heightened awareness during periods of physiological stress and in vulnerable subgroups [42,61]. Pharmacovigilance studies also highlight real-world reports of hypotension and volume depletion, while rare but serious events, such as necrotizing soft-tissue infections, have emerged in spontaneously reported data, prompting continued regulatory attention [3,62]. Although lower limb amputation risk appears inconsistent across large cohort studies, the possibility of increased risk in selected populations cannot be entirely excluded and warrants further investigation [46]. Importantly, most adverse events are mild to moderate in severity and manageable with appropriate clinical strategies, and they should not outweigh the well-established benefits of SGLT2 inhibitors when used in properly selected patients. Preventive measures—such as patient education on infection symptoms, individualized risk assessment, and careful monitoring—are critical to optimize safety and maximize therapeutic outcomes [63].

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