

Clinical Spectrum and Mechanism of Acute Kidney Injury in Patients with Diabetes Mellitus on SGLT-2 Inhibitors

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ABSTRACT: **Background:** Sodium-glucose cotransporter 2 inhibitors (SGLT2i) (such as canagliflozin, empagliflozin, and dapagliflozin) are widely used to treat patients with type 2 diabetes mellitus (T2DM) to improve glycemic, cardiovascular, and renal outcomes. However, based on post-marketing data, a warning label was added regarding possible occurrence of acute kidney injury (AKI).

Objectives: To describe the clinical presentation of T2DM patients treated with SGLT2i who were evaluated for AKI at our institution and to discuss the potential pathophysiologic mechanisms.

Methods: A retrospective study of a computerized database was conducted of patients with T2DM who were hospitalized or evaluated for AKI while receiving SGLT2i, including descriptions of clinical and laboratory characteristics, at our institution.

Results: We identified seven patients in whom AKI occurred 7–365 days after initiation of SGLT2i. In all cases, renin-angiotensin-aldosterone system blockers had also been prescribed. In five patients, another concomitant nephrotoxic agent (injection of contrast-product, use of nonsteroidal anti-inflammatory drugs or cox-2 inhibitors) or occurrence of an acute medical event potentially associated with AKI (diarrhea, sepsis) was identified. In two patients, only the initiation of SGLT2i was evident. The mechanisms by which AKI occurs under SGLT2i are discussed with regard to the associated potential triggers: altered trans-glomerular filtration or, alternatively, kidney medullary hypoxia.

Conclusions: SGLT2i are usually safe and provide multiple benefits for patients with T2DM. However, during particular medical circumstances, and in association with usual co-medications, particularly if baseline glomerular filtration rate is decreased, patients treated with SGLT2i may be at risk of AKI, thus warranting caution when prescribed.

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KEY WORDS: acute kidney injury (AKI), acute renal failure, renin-angiotensin-aldosterone system, sodium-glucose cotransporter 2 inhibitors (SGLT2i), type 2 diabetes mellitus (T2DM)

The development and approval of sodium-glucose cotransporter 2 inhibitors (SGLT2i), including canagliflozin, empagliflozin, and dapagliflozin, has proven to be successful in the management of type 2 diabetes mellitus (T2DM). SGLT2i provide benefits in terms of glycemic control, weight loss, blood pressure control, natriuretic effects, low risk of hypoglycemia, and renal protection. In addition, improved cardiovascular outcomes have been shown with empagliflozin [1]. Further analysis of the EMPA-REG cohort [2] revealed benefits in terms of renal protection over 4 years of follow-up in patients with T2DM. In that study, following an early reduction in glomerular filtration rate (GFR) in patients taking empagliflozin, a preservation of GFR was noted over time compared to untreated controls [2]. Similar results were published regarding the renal safety use of canagliflozin [3] and dapagliflozin [4]. Renal protection with SGLT2i may be indirect through modifications of cardiovascular risk factors. However, the improvement in renal outcomes likely also reflects reduced transglomerular pressure, manifested by the early 5% decline in GFR on average at the initiation of treatment [1].

An increasing number of reports of patients taking SGLT2i who developed acute kidney injury (AKI), some requiring hospitalization and dialysis, raises concerns regarding the safety of these medications under particular clinical settings, as was shown in a recent meta-analysis [5]. As a result, the U.S. Food and Drug Administration (FDA) revised the SGLT2i guidelines regarding the risk of AKI with canagliflozin and dapagliflozin [6], and the pharmaceutical company that manufactures empagliflozin modified its label warnings, included in the package insert of the medication [7].

In this article, we report on seven patients who were evaluated for evolving AKI while taking SGLT2i. These patients, treated with dapagliflozin or empagliflozin (canagliflozin is not yet available in Israel), presented with a spectrum of clinical problems or concomitant exposure to other medications that were likely to have triggered, or predisposed, patients to develop AKI. Our evaluation provides some insights as to the nature of the mechanisms possibly involved in SGLT2i-associated AKI.

PATIENTS AND METHODS

Our facility is a small community-oriented hospital (64,000 annual visits to the emergency department per year). We

conducted a retrospective study of the computerized database of hospitalized patients from February 2016 to January 2017 who had been admitted to our internal medicine department or ambulatory evaluated by one of our senior physicians. In our review of the medical records, we focused on the terms: acute renal failure, acute kidney injury, type 2 diabetes mellitus, SGLT2i, empagliflozin, and dapagliflozin. We then retrospectively analyzed the medical records of the involved patients and reconstituted the history of the observed kidney injury with regard to the initiation of SGLT2i.

Our study was approved by the Hadassah–Hebrew University Hospital ethics committee for clinical research. Formal consent from patients was not required.

RESULTS

Table 1 presents demographic data and results for the seven patients with T2DM in our study who experienced worsening renal function after recent prescription of SGLT2i. AKI occurred 7 to 365 days after initiation of SGLT2i. All patients had ischemic heart disease and were treated with renin-aldosterone-angiotensin system blockers (RAAS), which include either angiotensin converting enzyme inhibitors or angiotensinogen receptor blockers. Five patients had notable concurrent illnesses

and/or concomitant exposure to other potentially nephrotoxic medications, which likely contributed to their clinical presentation. However, in two patients (patients 6 and 7), no risk factor other than the initiation of SGLT2i was identified. The elevation of creatinine levels ranged from mild ($\times 1.3$ to $\times 1.6$ in patients 4, 5, 6, 7) to more severe ($\times 2.25$, $\times 3.2$, and $\times 4$ in patients 1, 2, and 3, respectively). GFR decline ranged from 13 to 69 ml/min/1.73m². The alteration in kidney function was transient and resolved with cessation of SGLT2i and concomitant nephrotoxic offenders, as well as with intravenous fluids in hospitalized patients (patients 1, 2, 3, 4, and 5).

DISCUSSION

We describe the cases of seven patients who developed AKI while taking SGLT2i, characterized by a GFR decline far beyond the commonly observed 2–5 ml/min/1.73m² reduction in GFR following initiation of these agents [1]. As GFR reduction related to reduced transglomerular pressure (TGP) is a reversible inherent feature of SGLT2i, it is tempting to assume that the latter contributed to the evolution of renal function impairment in these patients in conjunction with additional medical problems and/or concurrent medications. It is interesting to note that AKI was not reported as a significant adverse

Table 1. Features of patients treated with SGLT2i who were evaluated for acute kidney injury

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
Age, years	67	66	54	62	63	61	62
Gender	Male	Male	Female	Male	Male	Male	Male
Complications of DM	IHD, S/P CABG	IHD, CHF	DR, DN, IHD	DR, DN, microalbuminuria, IHD, S/P CABG	IHD	DR, DN, stage 3 CRF	DR, DN, proteinuria, stage 3 CRF, IHD, S/P CABG
SGLT2i	Empagliflozin 12.5 mg	Empagliflozin 25 mg	Dapagliflozin 10 mg	Empagliflozin 25 mg	Empagliflozin 25 mg	Empagliflozin 25 mg	Empagliflozin 10 mg
Time from initiation (days)	< 60	73	< 7	< 365	165	120	7
Latest Hb A1C, nmoI/mol	7.8 (62%)	6.8 (51%)	8.6 (70%)	8.4 (68%)	7.7 (61%)	8.1 (65%)	7.6 (60%)
S. creatinine (μmol/L)/GFR (ml/min.1.73m ²) baseline	87.5/80	87/81	61/94	65/115	76/96	123/55	159/41
S. creatinine (μmol/L)/GFR (ml/min.1.73m ²) peak	350/18	196/36	196/25	97/72	101/69	158/41	221/28
S. creatinine elevation/range of GFR decline (ml/min.1.73m ²)	$\times 4$ –62	$\times 2.25$ –45	$\times 3.1$ –69	$\times 1.5$ –43	$\times 1.6$ –27	$\times 1.3$ –15	$\times 1.4$ –13
S. creatinine (μmol/L)/GFR at discharge (ml/min.1.73m ²)	102/77	93/85	100/53	70/105	70/105	140/47	159/41
Possible contributing acute illness:							
Diarrhea	+	-	-	+	-	-	-
Urinary tract infection	-	-	+	+	+	-	-
Concomitant relevant medications:							
NSAIDs/Coxibs	-	+ celecoxib	+ etodolac	-	+etoricoxib	-	-
ACEi/ARB	+	+	+	+	+	+	+
Diuretics (Others)	-	Furosemide, hydrochlorothiazide	Spirinolactone	-	Radiocontrast agent (CT)	Furosemide	Furosemide

ACEi = angiotensin-converting enzyme inhibitor, AKI = acute kidney injury, ARB = angiotensinogen-receptor blocker, CHF = congestive heart failure, CRF = chronic renal failure, CT = computed tomography, DM = diabetes mellitus, DN = diabetic neuropathy, DR = diabetic retinopathy, GFR = glomerular filtration rate, IHD = ischemic Heart Disease, NA = not available, NSAIDs = nonsteroidal anti-inflammatory drugs, S = serum, SGLT2i = sodium-glucose cotransporter 2 inhibitors, S/P CABG = status post-coronary artery bypass graft

event in large clinical trials with empagliflozin [2], canagliflozin [3], and dapagliflozin [4], and that data regarding causality between AKI and the use of SGLT2i are conflicting. A recent meta-analysis [5] described acute renal impairment or failure in 511 out of 36,716 cases (1.4%) evaluated in 53 clinical trials. Dapagliflozin was significantly associated with increased risk of AKI, whereas empagliflozin was thought to be protective. In the FDA adverse events database [8] we also found a higher frequency of ARF in patients with T2DM treated with SGLT2i than in those not treated with the latter, with an overall reporting odds ratio of 1.68 (canagliflozin 7.4%, empagliflozin 4.7% and dapagliflozin 4.8%). In contrast, a recent observational study did not support an increased risk of AKI with SGLT2i [9].

Discerning the cause of AKI in patients is challenging, as other concomitant factors can explain the development of AKI. In our understanding, SGLT2i effects on renal physiology suggest that SGLT2i likely play a role in the occurrence of AKI [10]. First, SGLT2i induce volume depletion via diuresis, impair TGP, and reduce GFR by enhancing salt delivery to the distal nephron, activating tubule-glomerular feedback mechanisms and afferent renal artery vasoconstriction [11]. These effects are likely magnified in the presence of concomitant factors influencing effective blood volume and TGP, such as diuretics, and RAAS blockers, which reduce TGP via vasodilatation of efferent arterioles. Interestingly, in this view, all of our patients with suspected SGLT2i-associated AKI used RAAS blocking agents. Moreover, four patients used concomitant diuretics (patients 2, 3, 6, and 7), and two others (patients 1 and 4) had acute diarrhea.

SGLT2i may intensify kidney medullary hypoxia (KMH) as suggested by the increased renal hypoxic inducible factor (HIF) expression following SGLT2i initiation under experimental settings [12] and by the fact that patients treated with SGLT2i exhibit increased plasma erythropoietin concentrations, coupled with reticulocytosis [13], the former being a classical hypoxia/HIF-dependent gene. Indeed, intensification of medullary hypoxemia, detected by oxygen microelectrodes, was noted in diabetic and non-diabetic rats following SGLT inhibition [14], likely reflecting increased sodium delivery to distal nephron segments, with enhanced oxygen consumption by medullary thick ascending limbs, located in the outer medulla [10]. Together, these observations indirectly illustrate intensified hypoxia at the cortico-medullary junction, with enhanced regional erythropoietin transcription, triggered by HIF-2 stabilization [15]. In our report, three patients (patients 2, 3, and 5) were exposed to nonsteroidal anti-inflammatory drugs (NSAIDs), cox-2 inhibitors, or contrast product, which also induce KMH. Notably, two patients with baseline impaired GFR (patients 6 and 7), had no acute factors provoking AKI, other than the initiation of SGLT2i.

Our patients were overall exposed to two to four simultaneous factors reducing effective blood volume and TGP, and/or inducing KMH. This combination of factors likely contributed to the occurrence of AKI.

The limitations of the present report are inherent to retrospective analysis of limited available data and to the small number of patients, without matched control patient regarding co-morbidities, thus limiting the assumption of a direct causal relationship between the studied pharmacological agent (SGLT2i) and the occurrence of AKI. Furthermore, concomitant issues such as infections, dehydration, NSAID ingestion, or contrast media interference could have resulted in AKI irrespective to SGLT2i. Yet, it is conceivable that SGLT2i-induced volume depletion and altered renal microcirculation and oxygenation could have played a major role in predisposing these patients to AKI. Our observations are in accordance with the recent U.S. FDA-adjusted warnings for SGLT2i regarding the risk of AKI when using these medications.

CONCLUSIONS

Based on these observations and the available data, we believe clinicians should be aware that, while SGLT2i are safe and effective, they may increase in the risk of AKI, and that a number of measures could be considered to minimize this risk. Patients should be instructed to keep hydrated and avoid volume depletion. Physicians should consider closer monitoring of kidney function in patients with concomitant RAAS blockade and diuretics, especially those with impaired baseline GFR. Finally, it would be prudent to avoid concomitant administration of agents that induce KMH, such as NSAIDs or calcineurin inhibitors, and consider temporary withholding SGLT2i prior to radiocontrast studies.

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Capsule

Lewy body pathology and chronic traumatic encephalopathy associated with contact sports

Traumatic brain injury has been associated with increased risk of Parkinson disease and parkinsonism. Parkinsonism and Lewy body disease (LBD) can occur with chronic traumatic encephalopathy (CTE). To test whether contact sports and CTE are associated with LBD, **Adams** and colleagues compared deceased contact sports athletes (n = 269) to cohorts from the community (n = 164) and the Boston University Alzheimer disease (AD) Center (n = 261). Participants with CTE and LBD were more likely to have β -amyloid deposition, dementia, and parkinsonism than CTE alone ($P < 0.05$). Traditional and hierarchical clustering showed a similar pattern of LBD distribution in CTE compared to LBD alone that was most frequently neocortical, limbic, or brainstem. In the community-based cohort, years of contact sports play

were associated with neocortical LBD (odds ratio [OR] = 1.30 per year, $P = 0.012$), and in a pooled analysis a threshold of more than 8 years of play best predicted neocortical LBD (receiver operating characteristic analysis, OR = 6.24, 95% confidence interval = 1.5–25, $P = 0.011$), adjusting for age, gender, and *APOE* 4 allele status. Clinically, dementia was significantly associated with neocortical LBD, CTE stage, and AD. Parkinsonism was associated with LBD pathology but not CTE stage. Contact sports participation may increase the risk of developing neocortical LBD, and increased LBD frequency may partially explain extrapyramidal motor symptoms sometimes observed in CTE.

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Capsule

Zika virus as an oncolytic treatment of human neuroblastoma cells requires CD24

Neuroblastoma is the second most common childhood tumor. Survival is poor even with intensive therapy. In a search for therapies for neuroblastoma, **Mazar** and colleagues assessed the oncolytic potential of Zika virus. Recent studies have shown that neuronal progenitor cells are likely the human target of Zika virus. Neuroblastoma has been shown to be responsive to infection. In this study, the authors showed that neuroblastoma cells are widely permissive to Zika infection, revealing extensive cytopathic effects (CPE) and producing high titers of virus. However, a single cell line appeared poorly responsive to infection, producing undetectable levels of non-structural protein 1 (NS1), limited CPE, and low virus titers. A comparison of these poorly permissive cells to highly permissive neuroblastoma cells revealed a dramatic loss

in the expression of the cell surface glycoprotein CD24 in poorly permissive cells. Complementation of CD24 expression in these cells led to the production of detectable levels of NS1 expression after infection with Zika, as well as dramatic increases in viral titers and CPE. Complementary studies using the Zika virus index strain and a north African isolate confirmed these phenotypes. These results suggest a possible role for CD24 in host cell specificity by Zika virus and offer a potential therapeutic target for its treatment. In addition, Zika viral therapy can serve as an adjunctive treatment for neuroblastoma by targeting tumor cells that can lead to recurrent disease and treatment failure.

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“The greatest discovery of my generation is that a human being can alter his life by altering his attitudes of mind”

William James, (1842–1910), was an American philosopher and psychologist