Beyond Heart and Kidney Protection
Potential Uses of SGLT2 Inhibitors

By Jefferson L. Triozzi and L. Parker Gregg

Sodium-glucose cotransporter-2 (SGLT2) inhibitors demonstrate multiple effects beyond improving cardiovascular and kidney outcomes. Although much remains to be learned about the underlying mechanisms, early data suggest possible roles for SGLT2 inhibitors in the management of hyperglycemia, nephrolopathy, hyperammonemia, anemia, cardio-renal syndrome, and in kidney transplant recipients (Figure 1).

SGLT2 inhibitors may increase magnesium reabsorption in the nephron (Figure 2). In clinical trials, SGLT2 inhibitors led to an approximate 0.04–0.1 mM (0.10–0.24 mg/dL) increase in serum magnesium level when compared to placebo (1). This observed effect was generally within the physiologic range for serum magnesium level, but one case series suggests that SGLT2 inhibitors may have greater effect and therapeutic potential for patients with refractory urinary magnesium wasting (2). By potentially impacting magnesium reabsorption in multiple segments of the nephron, SGLT2 inhibitors may be useful for managing medication-induced urinary magnesium wasting, such as decreased paracellular reabsorption in patients taking loop diuretics or transient receptor potential melastatin type 6 (TRPM6) downregulation in patients taking thiadiazide diuretics or calcineurin inhibitors.

However, studies have not shown similar effects on handling of urinary calcium, another divalent cation (3). This may be because decreased urinary phosphate excretion in response to SGLT2 inhibition stimulates parathyroid hormone secretion (4). Despite the lack of substantial impact on urinary calcium excretion, the combined effects of SGLT2 inhibitors on urine volume, urinary phosphate excretion, and uric acid homeostasis may decrease the risk of nephrolithiasis (4–6).

The osmotic diuresis generated by SGLT2 inhibitors increases water excretion and may have a role in the management of hyponatremia. Empagliflozin was shown to raise plasma sodium concentration faster than placebo over 4 days in individuals with the syndrome of inappropriate antidiuretic hormone (SIADH) (7). Studies including more prolonged intervention and longer-term follow-up are needed, as transient changes in urine volume due to SGLT2 inhibitor initiation may not produce sustained effects on net water balance (8).

Clinical trials have shown higher hematocrit concentrations with SGLT2 inhibitors compared to placebo and decreased need for iron supplementation, erythropoietin-stimulating agents, or blood transfusions in those with concomitant diabetes and chronic kidney disease (9, 10).

In patients with type 2 diabetes, hyperglycemia causes maladaptive changes in the kidney that alter hypoxia-inducible factor pathways and impair erythropoiesis (10). Although incompletely understood, SGLT2 inhibitors may stimulate erythropoiesis by decreasing glucose accumulation in the cortical interstitium and by altering oxygen tension in the cortex and outer medulla (10–12). Less is known about the therapeutic role of SGLT2 inhibitors for anemia in patients without diabetes.

Given the heart and kidney protective effects of SGLT2 inhibitors, these agents are currently recommended in patients with chronic cardio-renal syndromes. In patients with stable heart failure, natriuresis after initiation of an SGLT2 inhibitor led to decreased blood and plasma volume without the concomitant neurohormonal activation or hypokalemia typically seen after loop diuretic administration (13). Less is known about the use of these drugs in patients with acute cardio-renal syndromes. In rats, SGLT2 inhibition may protect against cardio-renal acute kidney injury by reducing oxidative stress in the kidney (14). In patients with diabetes mellitus, SGLT2 inhibitors were associated with a decreased risk of acute kidney injury compared to other glucose-lowering medications (15–17). Understanding these relationships for patients with cardio-renal physiology will require studies incorporating biomarkers of kidney injury other than glomerular filtration rate, which may reflect hemodynamic changes rather than true kidney injury (18). Existing evidence is insufficient to support SGLT2 inhibitor use in cases of acute cardio-renal syndromes.

Although kidney transplant recipients were excluded from large SGLT2 inhibitor outcome trials, it is plausible that cardiovascular benefits could be extrapolated to this population in appropriate clinical contexts (19). One placebo-controlled randomized trial showed that empagliflozin lowered hemoglobin A1c by a median of −0.2% and body weight by a median of −2.5 kg in 44 kidney transplant recipients with posttransplant diabetes mellitus (20). Despite their immunosuppressed status, there was no increase in infections among patients receiving SGLT2 inhibitors, with three participants each in the...

**Figure 1. Potential clinical uses for SGLT2 inhibitors**

- **Hypomagnesemia**
  - Increase magnesium reabsorption in the nephron
- **Nephro lithiasis**
  - Affect urine volume, phosphate excretion, and uric acid homeostasis
- **Anemia**
  - Stimulate erythropoiesis
- **Cardiorenal syndrome**
  - Chronic benefits for heart and kidneys
- **Transplant recipients**
  - Long-term cardiovascular and kidney outcome trials are needed

Early data suggest several potential applications and proposed mechanisms for SGLT2 inhibitors beyond their well-known benefits for cardiovascular and kidney protection.

**Figure 2. Proposed effects of SGLT2 inhibitors on magnesium handling in the nephron**

TRPM6 activity may increase in the distal tubule, in part, stimulated by improved glycemic control and higher glucagon. The electrochemical gradient from increased sodium delivery may also contribute.

| Inhibition of SGLT2 leads to a positive luminal charge that may contribute to paracellular magnesium reabsorption in the proximal tubule. |
| Increased sodium delivery to the loop of Henle leads to increased activity of the NKCC with potassium recycling back into the tubular lumen via ROMK. This generates a positive luminal charge that may contribute to paracellular magnesium reabsorption. |

Several mechanisms potentially contribute to increased reabsorption of magnesium in the nephron. NKCC, sodium-potassium-2 chloride cotransporter; ROMK, renal outer medullary potassium channel; SGLT2, sodium-glucose cotransporter-2; TRPM6, transient receptor potential melastatin type 6.
emapagliflozin and placebo groups developing urinary tract infections and one participant in the emapagliflozin arm with a genital yeast infection. Larger studies are needed to evaluate efficacy and safety of SGLT2 inhibitors in this population and to better understand how these drugs affect allograft perfusion in kidney transplant recipients with impaired autoregulatory mechanisms.

Evidence supporting these potential uses of SGLT2 inhibitors is in early stages. It remains to be determined whether such uses differ among individual SGLT2 inhibitors. More research is needed to assess the mechanisms, durability, and clinical implications of these effects.

Jefferson L. Troszzi, MD, is a nephrology fellow at Vanderbilt University Medical Center in Nashville, TN. L. Parker Gregg, MD, MScS, is an Assistant Professor at Baylor College of Medicine and is with the Michael E. DeBakey VA Medical Center and Veterans Affairs Health Services Research and Development Center for Innovations in Quality, Effectiveness and Safety in Houston, TX.

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References


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