



SGLT2 Inhibitors for Treatment of Refractory Hypomagnesemia: A Case Report of 3 Patients

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In patients with urinary magnesium wasting, oral and intravenous supplementation often fail to adequately improve serum magnesium levels. Glucose intolerance and diabetes mellitus frequently accompany hypomagnesemia. Clinical trials examining inhibitors of the type 2 sodium glucose cotransporter (SGLT2) show small but significant increases in serum magnesium levels in diabetic patients. This report describes dramatic improvement in serum magnesium levels and associated symptoms after initiating SGLT2 inhibitor therapy in 3 patients with refractory hypomagnesemia and diabetes. Each patient received a different SGLT2 inhibitor: canagliflozin, empagliflozin, or dapagliflozin. One patient discontinued daily intravenous magnesium supplements and exhibited higher serum magnesium levels than had been achieved by magnesium infusion. 2 of the 3 patients exhibited reduced urinary fractional excretion of magnesium, suggesting enhanced tubular reabsorption of magnesium. These observations demonstrate that SGLT2 inhibitors can improve the management of patients with otherwise intractable hypomagnesemia, representing a new tool in this challenging clinical disorder.

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INTRODUCTION

Magnesium participates in more than 600 enzymatic reactions, contributes to nucleic acid and nucleotide triphosphate stability, and modulates cellular electrical activity.¹ Unsurprisingly, magnesium depletion results in wide-ranging effects, including cardiovascular, neuropsychiatric, and endocrine disorders, especially type 2 diabetes.²⁻⁵

Treatment of severe hypomagnesemia is often challenging. Gastrointestinal absorption limits oral supplementation.⁶ Intravenous magnesium infusion enhances urinary magnesium excretion, making serum magnesium level increases transient.⁷ Thus, patients with urinary magnesium wasting disorders often have persistent hypomagnesemia.

Hypomagnesemia provokes glucose intolerance and is associated with diabetes mellitus.⁵ Sodium glucose cotransporter 2 (SGLT2) inhibitors have been associated with small but significant increases in serum magnesium levels in patients with diabetes.⁸ We examined the effects of SGLT2 inhibitors in 3 patients with diabetes mellitus and intractable urinary magnesium wasting. Risks and benefits associated with the use of SGLT2 inhibitors were discussed with all patients, who agreed that the potential benefits outweighed the risks. All patients or their surrogates provided written consent for publication of their medical histories.

CASE REPORTS

Case 1

A man in his 60s experienced weakness and cramping after initiation of treatment with a thiazide diuretic for hypertension. His symptoms were attributed to hypomagnesemia that persisted even after discontinuation of the thiazide

therapy. Genetic evaluation revealed deletion of chromosome 17q12, including loss of hepatocyte nuclear factor 1 beta (HNF1B).⁹ Hypomagnesemia also likely contributed to numerous other disorders experienced by the patient (Table 1).

For 8 years, the patient received oral magnesium and amiloride therapy but experienced persistent symptomatic hypomagnesemia (Table 2 and Fig 1). He then began daily intravenous magnesium infusions in addition to oral supplements. These infusions were complicated by infection of his subcutaneous infusion port, leading to bacteremia and infectious endocarditis requiring 6 weeks of antibiotic therapy.

The patient was started on treatment with the SGLT2 inhibitor canagliflozin. Serum magnesium was measured weekly for the first 3 months. Within 8 weeks, his mean serum magnesium level demonstrated statistically significant improvement. Three months after starting canagliflozin therapy, magnesium infusions were discontinued. Oral supplements were continued with no change in dosing. Magnesium levels remained normal at 1.9 ± 0.1 mg/dL, which was significantly higher than historic levels receiving oral magnesium supplementation alone (1.4 ± 0.3 mg/dL; $P < 0.001$). He reported improved tolerance of physical exertion, fewer falls, reduced migraine frequency, and improved memory.

Fractional excretion of magnesium (FE_{Mg}) was examined (Fig 1B). The patient provided 24-hour urine collections to average out variation in urine magnesium concentrations associated with the relative timing of oral and intravenous magnesium dosing. The patient consumed a constant diet during each of his 24-hour urine collections. FE_{Mg} on canagliflozin therapy was lower than that measured either on oral or oral plus intravenous magnesium therapy.

Table 1. Patients With Hypomagnesemia

| | Patient 1 | Patient 2 | Patient 3 |
|----------------------------|---|---|---|
| Sex and age, y | Man, 60s | Woman, 60s | Woman, 20s |
| Cause of hypomagnesemia | 17q12 deletion | Unknown | <i>HNF1B</i> deletion |
| Associated disorders | | | |
| Neurologic | Cognitive deficit, cramping, weakness, falls, migraines, anxiety | Cramping, muscle weakness | Autism spectrum, learning disability, anxiety, migraines, cramping, weakness, wheelchair bound |
| Endocrine: | Hypokalemia, osteopenia, avascular necrosis of the hip, type 2 diabetes | Type 2 diabetes, hypercalcemia, osteoporosis with vertebral compression fracture | Type 2 diabetes |
| Cardiovascular: | Severe arterial calcification (coronary artery calcification score of 12,427) ^a | Hypertension | Hypertension |
| Therapy for hypomagnesemia | Maximum tolerated oral magnesium, plus loperamide for loose stools; intravenous magnesium (5 g/d, split into AM and PM infusions); amiloride (10 mg 3×/d) | Maximum tolerated oral magnesium; intravenous infusions previously discontinued due to transient efficacy; did not tolerate amiloride due to hyperkalemia | Oral magnesium (poor adherence due to nausea and loose stools); intravenous magnesium previously discontinued due to recurrent deep vein thrombosis and superior vena cava syndrome |
| SGLT2 inhibitor (dose) | Canagliflozin (300 mg/d) | Empagliflozin (10 mg/d) | Dapagliflozin (10 mg/d) |

Abbreviations: *HNF1B*, hepatocyte nuclear factor 1B; SGLT2, sodium glucose cotransporter 2.

^aThe dramatic coronary artery calcification experienced by patient 1 was previously reported as a novel finding in the 17q12 syndrome.²⁶

Case 2

A woman in her 60s with type 2 diabetes presented with fatigue, palpitations, and leg cramping due to hypomagnesemia. Sequencing of *HNF-1B* was normal (large deletions were not ruled out). Over 2 decades, oral magnesium therapy mitigated her symptoms but failed to normalize magnesium levels (Fig 1). Within 5 weeks of starting empagliflozin therapy, serum magnesium levels increased significantly. The patient experienced decreased daily insulin requirements and improved lower-extremity edema.

The patient was unable to provide a 24-hour urine collection immediately before starting empagliflozin therapy, so urine magnesium excretion was compared with historic measurements. Contemporary urine collections revealed higher daily magnesium excretion than historic collections, consistent with an increase in daily magnesium consumption. (Note that serum values shown in Tables 1 and 2 and Fig 1 represent measurements taken only during the 2-year period before initiation of an SGLT2 inhibitor or after initiation of the SGLT2 inhibitor. During this period, her oral magnesium regimen was unchanged.) FE_{Mg} on empagliflozin therapy resembled historic measurements (Fig 1B).

Case 3

A woman in her late 20s had experienced cognitive delay and headaches as a child and was diagnosed with severe hypomagnesemia as a consequence of de novo *HNF1B* deletion. She tolerated oral magnesium therapy poorly due to loose stools. Previous daily intravenous magnesium infusions had been discontinued due to recurrent catheter-

associated thrombosis and superior vena cava syndrome. She had type 2 diabetes mellitus with suspected diabetic nephropathy and microalbuminuria (albumin excretion, 50–163 mg/d). Her average estimated glomerular filtration rate of 106 ± 15 mL/min over the preceding 10 years had declined to 73 mL/min at the last measurement before initiation of dapagliflozin therapy. Initiation of dapagliflozin therapy was associated with increased serum magnesium levels, reduced FE_{Mg} (Table 2 and Fig 1), and improvement in muscle cramping and headaches.

DISCUSSION

These findings suggest that SGLT2 inhibitors can improve magnesium levels in patients with urinary magnesium wasting. For each patient, a statistically significant improvement in serum magnesium levels occurred within 8 weeks. (More frequent monitoring likely would have achieved statistical significance sooner.) The addition of an SGLT2 inhibitor was associated with a mean 0.36 ± 0.12 -mg/dL increase in serum magnesium levels across the 3 patients (comparing only periods when patients were not receiving regular intravenous supplementation). No patient experienced significant adverse reactions such as infection, hypoglycemia, or significant volume depletion.

Meta-analysis of diabetic patients receiving SGLT2 inhibitors has shown reduced hypomagnesemia in patients, with a mean increase in serum magnesium levels of 0.01 to 0.24 mg/dL.^{8,10} We observed a larger increase, and it is possible that patients with more severe hypomagnesemia experience a greater effect size. Patient 1 experienced higher serum magnesium levels with SGLT2 inhibition

Table 2. Metabolic Profiles and Changes With SGLT2 Inhibition

| | Patient 1 | | | Patient 2 | | | Patient 3 | | |
|-----------------|------------|------------|-----------|------------|-----------|------------|-----------|---|--|
| | Pre-SGLT2i | Pre-SGLT2i | On SGLT2i | Pre-SGLT2i | On SGLT2i | Pre-SGLT2i | On SGLT2i | | |
| Treatment | | | | | | | | | |
| Oral magnesium | + | + | + | + | + | + | + | | |
| IV magnesium | - | + | - | - | - | - | - | | |
| SGLT2 inhibitor | - | - | | + | - | + | - | + | |

| Blood Studies | Mean ± SD | P vs | Mean ± SD | P vs | Mean ± SD | Mean ± SD | P vs | Mean ± SD | Mean ± SD | P vs | Mean ± SD | Normal Range |
|---------------------------|--------------------|--------|---------------------|--------|---------------------|---------------------|--------|--------------------|---------------------|--------|--------------------|--------------|
| | (N) | SGLT2i | (N) | SGLT2i | (N) | (N) | SGLT2i | (N) | (N) | SGLT2i | (N) | |
| Na, mmol/L | 139 ± 3 (36) | 0.10 | 141 ± 2 (36) | 0.16 | 140 ± 1 (12) | 140 ± 2 (13) | 0.02 | 139 ± 1 (6) | 139 ± 2 (16) | 0.009 | 141 ± 2 (8) | 133-145 |
| K, mmol/L | 4 ± 0.3 (8) | <0.001 | 4.3 ± 0.3 (34) | 0.08 | 4.4 ± 0.2 (12) | 4.3 ± 0.2 (13) | 0.01 | 4.7 ± 0.4 (6) | 4.1 ± 0.2 (15) | 0.002 | 4.6 ± 0.4 (7) | 3.5-5.1 |
| Cl, mmol/L | 101 ± 1 (9) | 0.74 | 101 ± 2 (43) | 0.89 | 102 ± 1 (12) | 102 ± 1 (13) | <0.001 | 105 ± 1 (6) | 99 ± 1 (16) | 0.05 | 98 ± 1 (8) | 96-108 |
| tCO ₂ , mmol/L | 29.5 ± 2.3 (17) | <0.001 | 25 ± 1.6 (27) | 0.94 | 25 ± 0.9 (11) | 32.0 ± 2.4 (13) | 0.02 | 29.3 ± 1.6 (6) | 21.6 ± 2.5 (16) | 0.001 | 27.6 ± 3.8 (8) | 22-29 |
| BUN, mg/dL | 19.6 ± 2.7 (11) | <0.001 | 21.1 ± 3.4 (62) | <0.001 | 25.9 ± 3.1 (13) | 24 ± 3 (13) | 0.26 | 26 ± 3 (6) | 35 ± 8 (16) | | 34 (1) | 8-23 |
| Creatinine, mg/dL | 1.1 ± 0.1 (10) | 0.11 | 0.90 ± 0.10 (43) | <0.001 | 1.00 ± 0.10 (13) | 0.88 ± 0.04 (13) | <0.001 | 1.03 ± 0.11 (6) | 0.83 ± 0.10 (16) | <0.001 | 1.15 ± 0.03 (8) | 0.7-1.2 |
| Calcium, mg/dL | 9 ± 0.6 (9) | 0.18 | 9.4 ± 1.1 (64) | 0.63 | 9.2 ± 0.3 (12) | 10.7 ± 0.5 (13) | 0.25 | 10.5 ± 0.2 (6) | 9.6 ± 0.3 (16) | | 10.0 (1) | 8.6-10.2 |
| Albumin, mg/dL | 4.1 ± 0.1 (8) | 0.61 | 4.1 ± 0.2 (10) | 0.61 | 4.1 ± 0.2 (12) | 3.8 ± 0.1 (13) | 0.98 | 3.8 ± 0.1 (5) | 3.8 ± 0.3 (15) | | 3.8 (1) | 3.4-4.8 |
| Magnesium, mg/dL | 1.4 ± 0.3 (12) | <0.001 | 1.6 ± 0.2 (43) | <0.001 | 1.9 ± 0.1 (14) | 0.9 ± 0.1 (6) | <0.001 | 1.2 ± 0.1 (6) | 1.2 ± 0.2 (30) | <0.001 | 1.5 ± 0.1 (8) | 1.6-2.4 |

| 24-h urine studies | | | | | | | | | | | | |
|---------------------|------------------|------|--------------------|------|-------------------|-------------------|--|--------------------|---------------------|--------|-------------------|-------------|
| 24-h creatinine, mg | 1,175 (1) | | 1,173 ± 77 (4) | 0.46 | 1,220 ± 32 (2) | 1,350 ± 99 (3) | | 1,391 ± 126 (2) | 1,234 ± 212 (12) | 0.17 | 1,348 ± 80 (8) | 1,040-2,350 |
| 24-h Mg, mg | 325 ± 248 (3) | 0.86 | 432 ± 73 (4) | 0.27 | 361 ± 21 (2) | 127 ± 30 (3) | | 184 ± 18 (2) | 220 ± 132 (13) | 0.2 | 138 ± 17 (5) | 60.0-210 |
| 24-h glucose, g | | | 0.07 ± 0.01 (2) | | 39 (10) | | | | 0.07 ± 0.01 (2) | <0.001 | 50 ± 5 (6) | 0.02-0.09 |

Note: Laboratory measurements were performed using standard methods in local clinical laboratories. For each patient, laboratory and calculated values on SGLT2 inhibitor therapy were compared with prior values using unpaired *t* test. To convert values for urea nitrogen to mmol/L, multiply by 0.357; for glucose to mol/L, multiply by 0.0056; for creatinine to μmol/L, multiply by 88.4; for magnesium to mmol/L, divide by 2.43. Abbreviations: IV, intravenous; SD, standard deviation; SGLT2, sodium glucose cotransporter 2; SUN, serum urea nitrogen; tCO₂, total carbon dioxide.

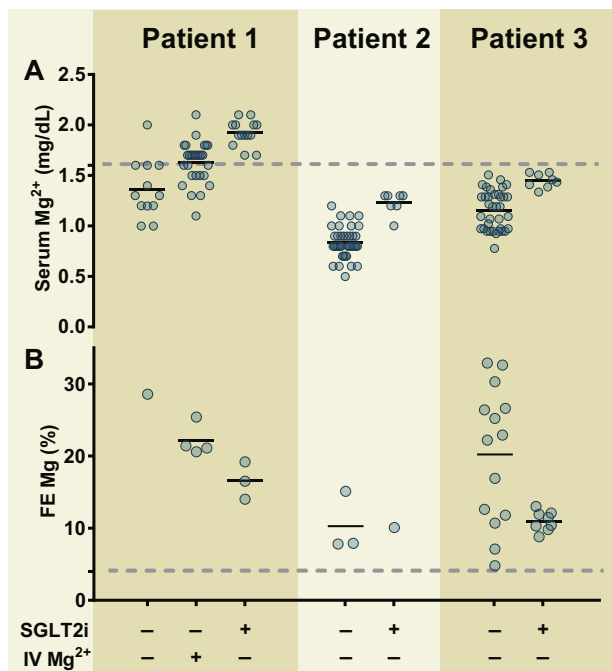


Figure 1. Sodium glucose cotransporter 2 (SGLT2) inhibition was associated with improved hypomagnesemia and reduction in fractional excretion of magnesium (FE_{Mg}) in 2 of 3 patients. (A) Serum magnesium levels on SGLT2 inhibitor (SGLT2i) therapy are compared with magnesium levels before initiation of these agents. To convert mg/dL to mmol/L, divide by 2.43. (B) FE_{Mg} before and after initiation of treatment with an SGLT2i. FE_{Mg} was calculated as $100 \cdot (\text{uMg} \cdot \text{sCr}) / (0.7 \cdot \text{sMg} \cdot \text{uCr})$, where uMg and uCr represent urinary magnesium and creatinine concentrations measured in 24-hour urine collections and sMg and sCr represent serum magnesium and creatinine levels, respectively. Dashed line at 4% represents upper limit of normal.²⁷ SGLT2 inhibition was associated with decreased FE_{Mg} in patient 1 ($32\% \pm 3\%$, $n = 4$ before vs $22\% \pm 2.5\%$, $n = 2$ on the drug; $P = 0.02$) and patient 3 ($20\% \pm 9\%$, $n = 14$ before vs $11\% \pm 1\%$, $n = 8$ on the drug; $P = 0.01$), but not patient 2 ($13\% \pm 4\%$, $n = 3$ before vs $13\% \pm 1\%$; $n = 2$, on empagliflozin). Abbreviation: IV Mg²⁺, daily intravenous magnesium supplementation.

than were achieved with daily intravenous supplementation.

In the management of refractory hypomagnesemia, potassium-sparing diuretics such as amiloride have previously represented a last resort.¹¹ In 2 reports, amiloride was associated with an increase in serum magnesium levels of ~ 0.25 mg/dL.^{12,13} Other studies found no change.^{14,15} Thus, SGLT2 inhibitors may be more effective at managing refractory hypomagnesemia than previously available modalities.

We observed reduced FE_{Mg} in 2 of the 3 patients. Patient 2 failed to demonstrate improvement in FE_{Mg}. However, this patient's laboratory values were compared with historic values, and the number of specimens provided for comparison was small. In the remaining patients,

diet and oral magnesium supplementation were better controlled, and patients provided more 24-hour urine collections for comparison. Reduction in FE_{Mg} in 2 patients suggests enhanced tubular reabsorption of magnesium, at least in some individuals with urinary magnesium wasting.

Several mechanisms may contribute to improved magnesium handling associated with SGLT2 inhibition. Our rationale for implementing these agents was to decrease electrogenic cotransport of sodium and glucose in the proximal tubule, in hopes that increased intraluminal electrical potential would promote magnesium reabsorption. Additionally, SGLT2 inhibitors induce extracellular fluid volume depletion and activation of the renin-angiotensin-aldosterone system.^{16,17} Acute angiotensin exposure enhances tubular magnesium uptake.^{16,17} This may occur as a consequence of solvent drag, similar to that described for calcium.¹⁸ Whether these effects persist over time remains unclear. Additionally, SGLT2 inhibition may influence magnesium reabsorption through other mechanisms, such as: (1) altered expression of magnesium transporters in kidney or gut, (2) hypertrophy or hyperplasia of tubular magnesium transporting segments, or (3) altered production of signaling agents (such as epidermal growth factor) that influence magnesium reabsorption.

Altered glucose metabolism may also influence magnesium handling. Glucagon promotes tubular magnesium reabsorption; increased glucagon levels due to urinary glucose wasting would increase tubular magnesium uptake.¹⁹ However, glucagon levels do not appear elevated in humans receiving SGLT2 inhibitors.²⁰ Insulin may also stimulate tubular magnesium reabsorption, and improvement in hyperinsulinemia associated with better glycemic control would increase rather than decrease magnesium excretion.²¹ Improved hyperinsulinemia could allow redistribution of magnesium out of cells, spuriously increasing serum magnesium levels and decreasing FE_{Mg}.²² However, euglycemic hyperinsulinemic clamp in humans reduced serum magnesium levels by only 0.1 mg/dL and resulted in absolute reduction in FE_{Mg} of less than 0.5%.²² Thus, it appears unlikely that changes in insulin or glucagon signaling fully explain the improvements we observe in magnesium handling, but studies performed under laboratory conditions could more conclusively address the contribution of this mechanism.

Reduced glomerular filtration of magnesium could also reduce urinary magnesium loss. SGLT2 inhibitor-associated reduction in glomerular filtration rate has been attributed to enhanced tubuloglomerular feedback, increasing afferent arteriolar tone.²³ New evidence also suggests reduced efferent arteriolar tone.²⁴ Either would reduce glomerular filtration. In the present study, unstable baseline glomerular filtration rates confounded calculation of changes in magnesium filtration due to SGLT2 inhibitors, and we are unable to say whether

hemodynamic changes contributed to increased serum magnesium levels.

Whether SGLT2 inhibitors could be used in hypomagnesemic patients without diabetes represents another important question. In the DAPA-HF trial, dapagliflozin was given to patients with heart failure, the majority of whom had no diabetes.²⁵ The trial saw no increase in adverse events, including infection and hypoglycemia. Thus, SGLT2 inhibition appears safe in nondiabetic patients. The authors did not report serum magnesium levels, and it remains to be seen whether SGLT2 inhibitors reduce urinary magnesium excretion in nondiabetic individuals.

The present study demonstrates that SGLT2 inhibitors can ameliorate refractory hypomagnesemia in patients with urinary magnesium wasting, potentially by enhancing renal tubular reabsorption of magnesium. These agents represent a potent new tool in the management of this challenging clinical disorder, with life-altering benefits for patients.

ARTICLE INFORMATION

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