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BRIEF REPORT

Effects of Canagliflozin on Serum Magnesium in Patients With Type 2 Diabetes Mellitus: A Post Hoc Analysis of Randomized Controlled Trials

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ABSTRACT

Introduction: The objective of this study was to evaluate the effects of canagliflozin, a sodium glucose co-transporter 2 inhibitor, on serum magnesium in hypomagnesemic patients with type 2 diabetes.

Methods: This post hoc analysis was based on pooled data from four placebo-controlled studies of canagliflozin ($N = 2313$). The proportion of patients with baseline serum magnesium <0.74 mmol/L who achieved serum magnesium ≥0.74 mmol/L at week 26 was evaluated.

Results: At week 26, canagliflozin 100 and 300 mg increased serum magnesium versus placebo in patients with baseline serum magnesium <0.74 mmol/L (17.0% and 19.0% vs 3.9%) and ≥0.74 mmol/L (4.9% and 7.0% vs −1.4%). More patients with baseline serum magnesium <0.74 mmol/L had serum magnesium ≥0.74 mmol/L at week 26 with canagliflozin 100 and 300 mg versus placebo (74.1% and 80.6% vs 28.8%).

Conclusions: Canagliflozin was associated with normalization of serum magnesium in hypomagnesemic patients with type 2 diabetes, potentially leading to improved cardiometabolic outcomes.

Clinical trial registration: ClinicalTrials.gov Identifiers, NCT01081834, NCT01106677, NCT01106625, NCT01106690.

Keywords: Canagliflozin; Cardiometabolic; Cardiovascular disease; Magnesium; Sodium glucose co-transporter; Type 2 diabetes

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INTRODUCTION

Many patients with type 2 diabetes have hypomagnesemia (serum magnesium <0.74 mmol/L); poor intestinal absorption and renal wasting of magnesium have been implicated in the pathophysiology [1]. Hypomagnesemic patients with type 2 diabetes show more rapid disease progression and decline in renal function than those with normal magnesium levels, and they are at increased risk for cardiometabolic complications and chronic kidney disease (CKD)

[1–3]. Hypomagnesemic patients with type 2 diabetes have reduced pancreatic β-cell activity and increased insulin resistance, which, in turn, lower serum magnesium levels as part of a "vicious circle" [1]. Hypomagnesemia is also an established risk factor for ventricular arrhythmia, which may be an indicator of future cardiovascular events or sudden cardiac death [4]. Increased magnesium levels have been shown to mitigate cardiovascular risk [5, 6].

In a systematic review and meta-analysis of randomized controlled trials, every 0.2 mmol/L increase in circulating magnesium was associated with a 30% reduction in cardiovascular disease risk; there was also a trend toward lower risks of ischemic heart disease and fatal ischemic heart disease [5]. A separate meta-analysis demonstrated that increased dietary magnesium intake was associated with a decreased risk of heart failure and stroke [6].

The sodium glucose co-transporter 2 (SGLT2) inhibitor canagliflozin has demonstrated clinically meaningful improvements in glycemic control, body weight, and blood pressure, with a favorable tolerability profile in patients with type 2 diabetes [7]. Canagliflozin has also been shown to increase serum magnesium levels [8], with minimal changes in its fractional excretion [9]. We evaluated the effects of canagliflozin on serum magnesium in patients with type 2 diabetes and hypomagnesemia.

METHODS

Study Design

This post hoc analysis was based on pooled data from four 26-week, placebo-controlled, phase 3 studies ($N = 2313$) that evaluated canagliflozin 100 and 300 mg in patients with type 2 diabetes (ClinicalTrials.gov Identifiers: NCT01081834, NCT01106677, NCT01106625, NCT01106690).

Endpoints/Assessments

Percentage change in serum magnesium at week 26 was evaluated in patients with baseline serum magnesium <0.74 and ≥0.74 mmol/L using data obtained from standard laboratory assessments during the individual trials. The proportion of patients with baseline serum magnesium <0.74 mmol/L who achieved serum magnesium ≥0.74 mmol/L at week 26 was determined.

Statistical Analyses

Data were from the modified intent-to-treat population (mITT), which consisted of all randomized patients who received ≥1 dose of study drug. The last observation carried forward approach was used to impute missing data at week 26. Percentage change from baseline in serum magnesium was analyzed using an analysis of covariance (ANCOVA) model, with treatment and study as fixed effects and the corresponding baseline serum magnesium value as a covariate. The model included terms for treatment (to assess treatment effect), baseline (to adjust for baseline differences), and study (to account for differences in the studies as the analysis was based on pooled data). Least squares (LS) mean differences and two-sided 95% confidence intervals (CIs) were determined for each canagliflozin dose versus placebo. The categorical endpoint of the proportion of hypomagnesemic patients with serum magnesium <0.74 mmol/L at baseline who achieved serum magnesium ≥0.74 mmol/L at week 26 was analyzed using a logistic regression model, with treatment and study as fixed effects and baseline serum magnesium value as a covariate. Odds ratios (ORs) and 95% CIs were estimated for the proportion of hypomagnesemic patients whose serum magnesium levels normalized at week 26 with canagliflozin versus placebo. Statistical testing of differences between canagliflozin and placebo was not prespecified for these analyses; therefore, P values are not reported.

Compliance with Ethics Guidelines

All study procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013.

Informed consent was obtained from all patients prior to their enrollment in the study.

RESULTS

Patients

Of 2313 patients in the mITT analysis set, mean baseline serum magnesium was 0.78 mmol/L (range 0.41–1.23 mmol/L [1–3 mg/dL]). In the overall population, 18.3% ($n = 424$) had serum magnesium <0.74 mmol/L (<1.8 mg/dL; hypomagnesemia), 80.7% ($n = 1867$) had serum magnesium 0.74–0.94 mmol/L (1.8–2.3 mg/dL; normal magnesium), and 1.0% ($n = 22$) had serum magnesium >0.94 mmol/L (>2.3 mg/dL; hypermagnesemia) at baseline; proportions were generally similar with canagliflozin 100 and 300 mg and placebo, respectively, in each serum magnesium category (hypomagnesemia: 20.2%, 16.9%, and 17.8%; normal magnesium: 78.8%, 82.3%, and 81.3%; hypermagnesemia: 1.1%, 0.8%, and 0.9%). Baseline characteristics were generally balanced across groups in patients with baseline serum magnesium <0.74 and ≥0.74 mmol/L (because of the small number of patients with hypermagnesemia, data for all patients with serum magnesium ≥0.74 mmol/L were pooled; Table 1).

Effects on Serum Magnesium

In the overall population, LS mean percentage changes from baseline in serum magnesium at week 26 were 8.1% and 9.3% with canagliflozin 100 and 300 mg versus −0.4% with placebo [8]. Among patients with baseline serum magnesium <0.74 mmol/L, LS mean percentage changes in serum magnesium at week 26 were 17.0%, 19.0%, and 3.9% with canagliflozin 100 and 300 mg and placebo, respectively (differences [95% CI] vs placebo of 13.0% [10.5, 15.6] and 15.1% [12.4, 17.7]; Fig. 1). Among patients with baseline serum magnesium ≥0.74 mmol/L, LS mean percentage changes in serum magnesium were 4.9%, 7.0%, and −1.4% with canagliflozin 100 and 300 mg and placebo, respectively (differences [95% CI] of 6.3% [5.5, 7.2] and 8.4% [7.6, 9.2]; Fig. 1). There were no patients with serum magnesium levels above the upper limit of normal (>1.27 mmol/L) in any treatment group at 26 weeks.

At week 26 in the canagliflozin 100 and 300 mg and placebo groups, 59 (7.2%), 33 (4.0%), and 117 (18.6%) patients had hypomagnesemia; 731 (88.7%), 738 (90.3%), and 505 (80.4%) patients had normal serum magnesium levels; and 34 (4.1%), 46 (5.6%), and 6 (1.0%) patients had hypermagnesemia, respectively. Overall, a higher proportion of patients with baseline serum magnesium <0.74 mmol/L had serum magnesium ≥0.74 mmol/L at week 26 with canagliflozin 100 and 300 mg versus placebo (74.1%, 80.6%, and 28.8%, respectively; Fig. 2). For hypomagnesemic patients, the likelihood of achieving serum magnesium ≥0.74 mmol/L was 10 and 14 times greater with canagliflozin 100 and 300 mg versus placebo.

DISCUSSION

Hypomagnesemia is common in patients with type 2 diabetes (14–48%) and has been identified as an independent risk factor for cardiovascular disease and CKD [1–3]. In particular, hypomagnesemic individuals can develop ventricular arrhythmias, which may lead to serious cardiovascular outcomes, including sudden cardiac death [4, 10–12]. Evidence suggests that increases in circulating magnesium are associated with a lower risk of cardiovascular disease; this may be related to antiarrhythmic and anti-ischemic effects in the heart, as well as beneficial effects on endothelial tissue and vascular smooth muscle cells (e.g., enhanced vasodilation, reduced inflammation) [5]. In this analysis, canagliflozin treatment increased serum magnesium over 26 weeks and normalized magnesium levels in hypomagnesemic patients with type 2 diabetes.

Results from the current analysis are consistent with a recent meta-analysis of 18 randomized controlled trials of SGLT2 inhibitors in patients with type 2 diabetes, suggesting that the impact on serum magnesium levels may be a class effect [13]. Dose-dependent increases in magnesium were seen with canagliflozin 100

Table 1 Baseline demographic and disease characteristics

Characteristic[a]	Serum Mg <0.74 mmol/L (hypomagnesemia)				Serum Mg ≥0.74 mmol/L (normal Mg/hypermagnesemia)			
	PBO (n = 115)	CANA 100 mg (n = 168)	CANA 300 mg (n = 141)	Total (N = 424)	PBO (n = 531)	CANA 100 mg (n = 665)	CANA 300 mg (n = 693)	Total (N = 1889)
Sex, n (%)								
Male	39 (33.9)	74 (44.0)	54 (38.3)	167 (39.4)	295 (55.6)	334 (50.2)	350 (50.5)	979 (51.8)
Female	76 (66.1)	94 (56.0)	87 (61.7)	257 (60.6)	236 (44.4)	331 (49.8)	343 (49.5)	910 (48.2)
Age, years	57.6 (9.5)	58.3 (10.1)	56.3 (9.8)	57.5 (9.8)	56.0 (9.9)	55.3 (10.0)	55.6 (9.5)	55.6 (9.8)
Race, n (%)[b]								
White	88 (76.5)	140 (83.3)	112 (79.4)	340 (80.2)	382 (71.9)	451 (67.8)	498 (71.9)	1331 (70.5)
Black/African American	5 (4.3)	4 (2.4)	13 (9.2)	22 (5.2)	23 (4.3)	39 (5.9)	35 (5.1)	97 (5.1)
Asian	10 (8.7)	10 (6.0)	10 (7.1)	30 (7.1)	72 (13.6)	93 (14.0)	90 (13.0)	255 (13.5)
Other[c]	12 (10.4)	14 (8.3)	6 (4.3)	32 (7.5)	54 (10.2)	82 (12.3)	70 (10.1)	206 (10.9)
Ethnicity, n (%)[b]								
Hispanic/Latino	31 (27.0)	37 (22.0)	27 (19.1)	95 (22.4)	144 (27.1)	176 (26.5)	194 (28.0)	514 (27.2)
Not Hispanic/Latino	84 (73.0)	129 (76.8)	114 (80.9)	327 (77.1)	387 (72.9)	486 (73.1)	495 (71.4)	1368 (72.4)
Other[d]	0	2 (1.2)	0	2 (0.5)	0	3 (0.5)	4 (0.6)	7 (0.4)
HbA1c, %	8.1 (1.0)	8.2 (1.0)	8.2 (1.0)	8.2 (1.0)	8.0 (0.9)	8.0 (0.9)	7.9 (0.9)	8.0 (0.9)
HbA1c, mmol/mol[e]	65 (10.9)	66 (10.9)	66 (10.9)	66 (10.9)	64 (9.8)	64 (9.8)	63 (9.8)	64 (9.8)
Body weight, kg	91.8 (25.9)	93.6 (22.3)	90.9 (20.5)	92.2 (22.8)	88.7 (20.7)	88.8 (22.2)	88.0 (22.3)	88.5 (21.8)
BMI, kg/m^2	33.8 (7.7)	33.8 (6.4)	33.1 (6.0)	33.6 (6.6)	31.5 (6.0)	31.9 (6.4)	31.7 (6.6)	31.7 (6.3)
Waist circumference, cm	107.9 (18.3)	108.8 (15.8)	107.8 (14.9)	108.2 (16.2)	104.7 (14.9)	105.1 (15.6)	104.3 (14.8)	104.7 (15.1)
eGFR, mL/min/1.73 m^2	86.6 (17.9)	87.1 (20.2)	87.7 (18.1)	87.1 (18.9)	87.1 (20.3)	88.6 (18.7)	89.0 (19.0)	88.3 (19.3)
Duration of type 2 diabetes, years	9.4 (6.3)	9.5 (6.6)	9.3 (7.2)	9.4 (6.7)	7.1 (6.1)	6.6 (5.4)	7.0 (5.9)	6.9 (5.8)

Mg magnesium, *PBO* placebo, *CANA* canagliflozin, *BMI* body mass index, *eGFR* estimated glomerular filtration rate, *SD* standard deviation

[a] Data are mean (SD) unless otherwise indicated

[b] Percentages may not total 100.0% because of rounding

[c] Includes American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, multiple, other, unknown, and not reported

[d] Includes not reported and unknown

[e] HbA1c values in % were converted to mmol/mol using the National Glycohemoglobin Standardization Program (NGSP) harmonized HbA1c conversion tool (http://www.ngsp.org/convert1.asp)

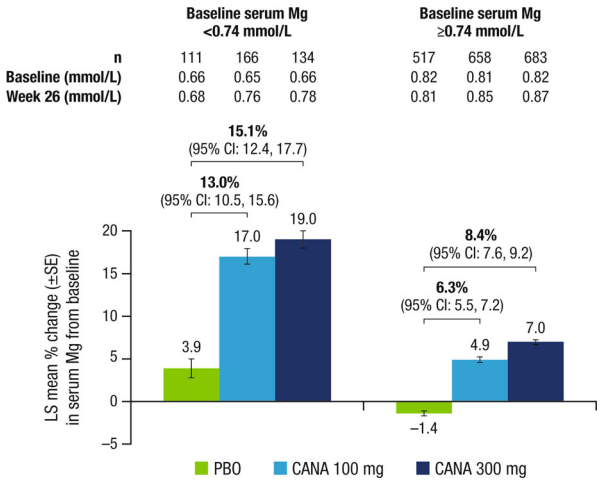

Fig. 1 Percentage change from baseline in serum magnesium at week 26. *Mg* magnesium, *CI* confidence interval, *LS* least squares, *SE* standard error, *PBO* placebo, *CANA* canagliflozin

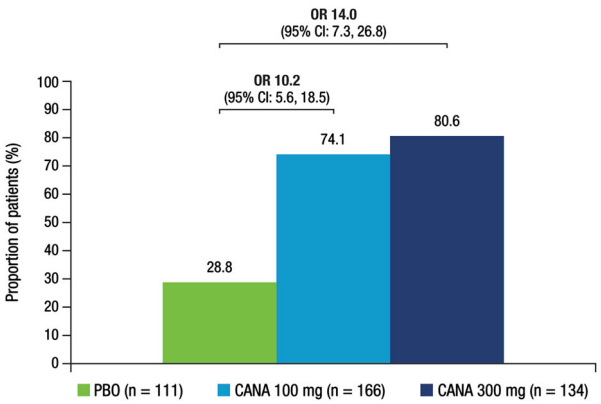

Fig. 2 Proportion of patients with baseline serum magnesium <0.74 mmol/L who achieved serum magnesium ≥0.74 mmol/L at week 26. *OR* odds ratio, *CI* confidence interval, *PBO* placebo, *CANA* canagliflozin

and 300 mg (0.06 vs 0.09 mmol/L); similar changes were observed with dapagliflozin 10 mg (0.1 mmol/L), empagliflozin 10 and 25 mg (0.04 vs 0.07 mmol/L), and ipragliflozin 50 mg (0.05 mmol/L) [13]. Of note, the meta-analysis results were based on data from patients with normal renal function, but a sensitivity analysis including data from two trials in patients with CKD showed that the overall findings were robust [13]. Canagliflozin has also demonstrated serum magnesium improvements in patients with type 2 diabetes and CKD (eGFR ≥30 and <50 mL/min/1.73 m^2) [14, 15]. Over 26 weeks of treatment, increases in serum magnesium were seen with canagliflozin 100 and 300 mg (9.4% vs 14.6%), whereas no change was seen with placebo (0.0%; baseline, 0.8 mmol/L for all) [14].

Abnormal elevations of serum magnesium have been linked to adverse cardiovascular outcomes in certain populations (e.g., heart failure, critically ill, or on hemodialysis) [16–18]. In this analysis, there was a small increase from baseline in the number of patients with hypermagnesemia in the canagliflozin groups at week 26, but no patients had serum magnesium levels above the upper limit of normal (>1.27 mmol/L). It is important to note that canagliflozin is not indicated for use in patients with severe renal impairment or end-stage renal disease or who are on dialysis [19].

The mechanism for the observed effects of canagliflozin on serum magnesium is unclear. It is unlikely that the increases in serum magnesium seen with canagliflozin are attributable to glycemic improvements, as increases in serum magnesium have not been reported with other antihyperglycemic agents, including sitagliptin and glimepiride, in head-to-head studies with canagliflozin (data on file and [20]). A possible explanation is that canagliflozin treatment is associated with improvements in insulin sensitivity (measured by changes in glucosuria-corrected oral glucose insulin sensitivity [$OGIS_c$] index values [21]), which may increase magnesium levels by interrupting the cycle of hypomagnesemia induced by insulin resistance. And while bone storage is involved in magnesium homeostasis, it is unlikely that increased magnesium levels are due to leaching from bone, as bone mineral density remains relatively unchanged with canagliflozin treatment over 2 years [22]. Another consideration is that SGLT2 inhibitors have been shown to increase plasma glucagon levels [23, 24], which may increase magnesium reabsorption in the distal convoluted tubule (DCT) [25]. Finally, the observed increase in serum magnesium may be related to canagliflozin acting on ion channels in the DCT (e.g., TRPM6/TRPM7), which have been found to modulate urinary magnesium excretion [26].

This analysis was strengthened by the use of a large, pooled dataset. At baseline, approximately 18% of patients were hypomagnesemic, which is representative of the general type 2 diabetes population [1]. One potential limitation of this analysis was that there were no restrictions on the use of drugs known to alter magnesium homeostasis (e.g., diuretics, proton pump inhibitors, antimicrobials) [1], which may have impacted serum magnesium levels. However, canagliflozin treatment has demonstrated consistent increases in serum magnesium across a broad range of patients with type 2 diabetes with varying degrees of background diuretic use, including the current analysis (approximately 23% of patients were on diuretics) and a separate analysis of patients with eGFR $\geq$45 and <60 mL/min/1.73 m^2 (approximately 50% of patients were on diuretics) [8]. Another potential limitation was that intracellular magnesium levels were not measured. Intracellular magnesium has been proposed to better reflect magnesium homeostasis than serum magnesium, as approximately 99% of magnesium is stored within bone, muscle, and other soft tissues; however, serum magnesium remains widely used and may be a more practical measure for clinicians who treat patients with type 2 diabetes.

CONCLUSIONS

Canagliflozin was associated with normalization of serum magnesium levels in hypomagnesemic patients with type 2 diabetes, which may lead to improved cardiometabolic outcomes and a reduced risk of arrhythmia. Results from ongoing, large-scale outcomes trials will help to define the potential benefits of canagliflozin on cardiovascular health and risk of CKD.

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Compliance with Ethics Guidelines. All study procedures followed were in accordance

with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013. Informed consent was obtained from all patients prior to their enrollment in the study.

Data Availability. The datasets analyzed for the current analysis are available from the corresponding author on reasonable request.

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