Correction of hypomagnesemia by dapagliflozin in patients with type 2 diabetes: A post hoc analysis of 10 randomized, placebo-controlled trials

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Aims: Hypomagnesemia (serum magnesium [Mg] <0.74 mmol/L [<1.8 mg/dL]) is commonly observed in patients with type 2 diabetes (T2D). This study investigated the effect of treatment with dapagliflozin 10 mg on Mg concentrations in patients with T2D.

Methods: In this post hoc analysis, we used pooled data from 10 placebo-controlled studies of dapagliflozin over 24 weeks of treatment in patients with T2D. We evaluated the change in Mg in patients receiving dapagliflozin vs. placebo overall, and in subgroups with baseline hypomagnesemia and normal/hypermagnesemia (≥0.74 mmol/L [≥1.8 mg/dL]). We determined the proportion of patients with baseline hypomagnesemia who achieved Mg ≥0.74 mmol/L (≥1.8 mg/dL).

Results: A total of 4398 patients with T2D were included. The mean change from baseline to week 24 in Mg was −0.06 mmol/L (95% confidence interval [CI]: 0.05, 0.06). The proportion of patients with Mg within the population reference range after 24 weeks of treatment was significantly higher with dapagliflozin vs. placebo; difference, 47.8% (95% CI: 41.4, 53.9). The proportion of patients displaying hypermagnesemia did not increase with dapagliflozin treatment.

Conclusions: Treatment with dapagliflozin 10 mg resulted in correction of Mg concentrations in patients with T2D and hypomagnesemia.

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1. Introduction

Magnesium (Mg) is the second most common intracellular cation after calcium and plays a key role in multiple physiological processes, serving as a cofactor in >300 enzymatic reactions, including those responsible for regulating glycemic control, blood pressure (BP), and lipid peroxidation. Hypomagnesemia (serum Mg <0.74 mmol/L [<1.8 mg/dL]) is observed in 14–48% of patients with type 2 diabetes (T2D) and is associated with increased insulin resistance, altered cellular glucose transport, and reduced pancreatic insulin secretion. In patients with T2D, hypomagnesemia may contribute to a worsening of insulin resistance, which can then further reduce serum Mg concentrations. Hypomagnesemia in patients with T2D is associated with poor glycemic control; patients have higher levels of fasting and postprandial plasma glucose, along with higher glyated hemoglobin (HbA1c), compared with patients with normal serum Mg concentrations. Additionally, hypomagnesemia is associated with a more rapid decline in kidney function in patients with T2D and is a risk factor for cardiovascular disease, end-stage kidney disease (ESKD), retinopathy, nephropathy, and foot ulcers. Patients with T2D and hypomagnesemia demonstrate more frequent premature ventricular complexes and may be at an increased risk of sudden cardiac death.

Sodium-glucose co-transporter 2 inhibitors (SGLT2i) are a class of oral glucose-lowering agents recently approved for the treatment of T2D. SGLT2 block renal reabsorption of glucose, promoting glycosuria and lowering of blood glucose without stimulating insulin release, thus minimizing the risk of hypoglycemia. Notably, the antihyperglycemic effect of SGLT2i is accompanied by cardiovascular and renal protection, including significant reductions in systolic and diastolic BP (SBP and DBP). Accordingly, SGLT2i are recommended as the preferred treatment for patients with T2D with heart failure or chronic kidney disease.

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failing to meet target HbA1c with metformin and lifestyle modification. Recent evidence suggests that SGLT2i treatment, either alone or in combination with other agents, corrects low serum Mg concentrations in patients with T2D, potentially contributing to improved cardiometabolic outcomes. Building on this emerging evidence, the primary objective of the current post hoc analysis was to quantify the effect of dapagliflozin treatment on serum Mg concentrations in patients with T2D. Furthermore, it remains to be evaluated if the established BP-lowering effect of SGLT2i differs in patients with and without hypomagnesemia. Therefore, a secondary objective of the current study was to explore any potential differences in BP response across serum Mg subgroups.

2. Materials and methods

2.1. Study design

This post hoc analysis evaluated the effect of dapagliflozin 10 mg once daily on serum Mg concentrations over 24 weeks across 10 placebo-controlled, double-blind clinical trials in patients with T2D (N = 4398). Two trials included dapagliflozin monotherapy treatment arms,23-25 dapagliflozin was also evaluated as combination therapy with metformin,26-28 glimepiride,29 pioglitazone,30 sitagliptin with or without metformin,31 or insulin.32 All trials were part of the dapagliflozin clinical development program, were not designed to examine cardiovascular events, and did not include measures or estimates of dietary or supplemental Mg intake. The trial protocols did not include specific dietary recommendations or restrictions regarding dietary or supplemental Mg. Information on patient ethnicity was not recorded across all trial sites and is therefore not reported in the current analysis. Further details of the clinical trials are listed in Supplementary Table 1.

2.2. Outcomes

We evaluated the change in serum Mg over 24 weeks in patients receiving dapagliflozin 10 mg vs. placebo using laboratory assessment data collected during the individual clinical trials. Blood samples were collected and analyzed at a central laboratory during the trials as part of standard clinical trial safety assessments; serum Mg was collected at weeks 1, 4, 12, 16, 20, and 24. We also evaluated change in serum Mg stratified by baseline hypomagnesemia (<0.74 mmol/L [<1.8 mg/dL]) and normal/hypermagnesemia (≥0.74 mmol/L [≥1.8 mg/dL]) and by baseline estimated glomerular filtration rate (eGFR) <60 and ≥60 mL min⁻¹ 1.73 m⁻², calculated with the Modification of Diet in Renal Disease Study equation. We determined the proportion of patients with baseline serum Mg <0.74 mmol/L (<1.8 mg/dL) who achieved serum Mg ≥0.74 mmol/L (≥1.8 mg/dL) at week 24, along with the proportions of patients with hypermagnesemia (>1.05 mmol/L [>2.6 mg/dL]) and >1.27 mmol/L [>3.6 mg/dL]). We also evaluated changes from baseline to week 24 in SBP and DBP (mm Hg) and heart rate (HR) (beats per minute [bpm]) in the two treatment groups, along with the two serum Mg subgroups (<0.74 mmol/L [<1.8 mg/dL] and ≥0.74 mmol/L [≥1.8 mg/dL]). Finally, we evaluated the occurrence of adverse events (AEs), including those according to the Medical Dictionary for Regulatory Activities System Organ Class “cardiac disorders.”

2.3. Statistical analyses

Descriptive statistics are used for presenting baseline characteristics and safety data. For efficacy parameters, we derived mean changes from baseline values and 95% confidence intervals (CIs) using a longitudinal repeated-measures mixed model with fixed terms for study, treatment, week, subgroup, week-by-treatment interaction, treatment-by-subgroup interaction, and treatment-by-week-by-subgroup interaction, along with the fixed covariates of baseline, baseline-by-study, and baseline-by-week interactions. We used the Kenward-Roger method to approximate the degrees of freedom in the mixed model. In the event that the model(s) did not converge, we employed either the Satterthwaite approximation or re- ran models using the Kenward-Roger method with the baseline-by-study term removed. The Exact method was used to calculate the CIs within treatment and for the difference between treatments with respect to the proportion of patients with baseline serum Mg <0.74 mmol/L (<1.8 mg/dL) achieving serum Mg ≥0.74 mmol/L (≥1.8 mg/dL) at 24 weeks using the last-observation-carried-forward (LOCF) method. Week 24 LOCF was derived as the last value obtained during the short-term period, regardless of scheduled or nonscheduled.

3. Results

A total of 4398 patients were included in the study, with 2164 and 2234 patients randomized to placebo and dapagliflozin 10 mg, respectively. Of the overall population, 17.6% (n = 773) of patients had hypomagnesemia (serum Mg <0.74 mmol/L [<1.8 mg/dL]), and 82.4% (n = 3625) of patients had normal/hypermagnesemia (serum Mg ≥0.74 mmol/L [≥1.8 mg/dL]). Baseline characteristics were quite similar between the subgroups; however, the proportion of women was higher in the hypomagnesemia subgroup vs. the normal/hypermagnesemia subgroup, and patients with hypomagnesemia had a longer mean duration of diabetes compared with patients with normal/hypermagnesemia. Additionally, a larger proportion of patients with hypomagnesemia had a history of cardiovascular disease and/or heart failure, hypertension, dyslipidemia, and peripheral vascular disease and were more often treated with diuretics compared with patients with normal/hypermagnesemia (Table 1).

In patients receiving dapagliflozin 10 mg, the difference from placebo in increase in mean serum Mg from baseline to week 24 was 0.06 mmol/L in the overall T2D population, 0.08 mmol/L in patients with hypomagnesemia, and 0.05 mmol/L in patients with normal/hypermagnesemia (Table 2). In patients with hypomagnesemia at baseline, serum Mg increased to within the population reference range at 24 weeks in 29.5% (n = 108/366) and 77.3% (n = 307/397) of patients randomized to placebo and dapagliflozin 10 mg, respectively. The difference between treatments in patients achieving normal serum Mg was 47.8% (95% CI: 41.4, 53.9) (Fig. 1). At 24 weeks, the proportion of patients with baseline serum Mg ≥0.74 mmol/L (≥1.8 mg/dL) with hypermagnesemia (serum Mg >1.05 mmol/L [>2.6 mg/dL]) was low: 0.7% (n = 13/1781) and 1.7% (n = 31/1811) in the placebo and dapagliflozin 10 mg groups, respectively (Fig. 2).

In patients receiving dapagliflozin 10 mg, the adjusted changes in mean serum Mg were similar in patients with eGFR below and above 60 mL min⁻¹ 1.73 m⁻² at baseline: 0.08 mmol/L in patients with hypomagnesemia and 0.05–0.06 mmol/L in patients with normal/hypermagnesemia (Fig. 3A and B).

The adjusted changes from baseline to week 24 in mean SBP were −0.85 mm Hg (95% CI: −1.39, −0.32) and −3.87 mm Hg (95% CI: −4.40, −3.35) with placebo and dapagliflozin 10 mg, respectively; difference, −3.02 mm Hg (95% CI: −3.73, −2.31). The adjusted changes from baseline to week 24 in mean DBP were −0.45 mm Hg (95% CI: −0.78, −0.12) and −1.77 mm Hg (95% CI: −2.10, −1.45) with placebo and dapagliflozin 10 mg, respectively; difference, −1.33 mm Hg (95% CI: −2.27, −0.88). The adjusted changes from baseline to week 24 in mean HR were 0.69 bpm (95% CI: 0.32, 1.06) and −0.06 bpm (95% CI: −0.41, 0.30) with placebo and dapagliflozin 10 mg, respectively; difference, −0.75 bpm (95% CI: −1.24, −0.25). In the dapagliflozin 10 mg group, no clinically meaningful differences were observed in placebo-adjusted mean changes in SBP, DBP, and HR in patients with hypomagnesemia vs. patients with normal/hypermagnesemia (Supplementary Fig. 1).
4. Discussion

This post hoc analysis included 10 clinical trials with a pooled sample size of >4000 patients providing a robust analysis of the effect of treatment with dapagliflozin 10 mg on serum Mg concentrations in patients with T2D. The prevalence of hypomagnesemia in patients with T2D (17.6%) reported in this study was within the 14%–48% range previously reported. As predicted by the literature, a larger proportion of patients with baseline hypomagnesemia had a history of cardiovascular disease and/or heart failure, dyslipidemia, and peripheral arterial disease/peripheral vascular disease. Mg levels were more pronounced in patients with normal/hypermagnesemia vs. those with hypermagnesemia. The proportion of patients with hypomagnesemia at baseline whose serum Mg was within the population reference range after 24 weeks of treatment was significantly higher with dapagliflozin 10 mg vs. placebo. We observed very low rates of hypomagnesemia at baseline and week 24. Overall, Mg concentrations were similar between the treatment groups (Supplementary Table 2).

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| Table 1 | Baseline characteristics.
<table>
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<td></td>
<td>Hypomagnesemia serum Mg &lt; 0.74 mmol/L (≤ 1.8 mg/dL)</td>
<td>Normal/hypermagnesemia serum Mg ≥ 0.74 mmol/L (≥ 1.8 mg/dL)</td>
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<tr>
<td></td>
<td>Placebo</td>
<td>N = 370</td>
<td>Placebo</td>
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<td></td>
<td>Dapagliflozin 10 mg</td>
<td>N = 403</td>
<td>Dapagliflozin 10 mg</td>
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<tr>
<td>Age, years</td>
<td>61.2 (8.9)</td>
<td>60.8 (9.6)</td>
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<td>Women, n (%)</td>
<td>182 (49.2)</td>
<td>186 (46.7)</td>
<td>728 (40.6)</td>
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<td>Race, n (%)</td>
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<tr>
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<td>368 (91.6)</td>
<td>1529 (85.2)</td>
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<td>Black or African American</td>
<td>13 (3.5)</td>
<td>14 (3.5)</td>
<td>56 (3.1)</td>
</tr>
<tr>
<td>Asian</td>
<td>13 (3.5)</td>
<td>9 (2.2)</td>
<td>138 (7.7)</td>
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<tr>
<td>Other*</td>
<td>12 (3.2)</td>
<td>11 (2.7)</td>
<td>71 (4.0)</td>
</tr>
<tr>
<td>Duration of T2D, years</td>
<td>11.1 (8.1)</td>
<td>11.5 (8.3)</td>
<td>8.6 (7.9)</td>
</tr>
</tbody>
</table>

Data are represented as mean (SD) unless otherwise stated.

ACEi/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; bpm, beats per minute; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; Hba1c, glycated hemoglobin; Mg, magnesium; N#, number of randomized patients with nonmissing baseline and week 24 values; SD, standard deviation.; T2D, type 2 diabetes.

* Includes patients with a reported race of American Indian/Alaska Native, Native Hawaiian/other Pacific Islander, or other.

4. Discussion

This post hoc analysis included 10 clinical trials with a pooled sample size of >4000 patients providing a robust analysis of the effect of treatment with dapagliflozin 10 mg on serum Mg concentrations in patients with T2D. The prevalence of hypomagnesemia in patients with T2D (17.6%) reported in this study was within the 14%–48% range previously reported. As predicted by the literature, a larger proportion of patients with baseline hypomagnesemia had a history of cardiovascular disease and/or heart failure, dyslipidemia, and peripheral arterial disease/peripheral vascular disease. Mg levels were more pronounced in patients with normal/hypermagnesemia vs. those with hypermagnesemia. The proportion of patients with hypomagnesemia at baseline whose serum Mg was within the population reference range after 24 weeks of treatment was significantly higher with dapagliflozin 10 mg vs. placebo. We observed very low rates of hypomagnesemia at baseline and week 24. Overall, Mg concentrations were similar between the treatment groups (Supplementary Table 2).

Table 2

| Table 2 | Adjusted changes from baseline to week 24 in serum Mg levels. |
|---------|---------|---------|
|         | Overall T2D population | Hypomagnesemia serum Mg < 0.74 mmol/L (≤ 1.8 mg/dL) | Normal/hypermagnesemia serum Mg ≥ 0.74 mmol/L (≥ 1.8 mg/dL) |
|         | Placebo | Dapagliflozin 10 mg | Placebo | Dapagliflozin 10 mg | Placebo | Dapagliflozin 10 mg |
| N# | 1849 | 1956 | 306 | 353 | 1542 | 1603 |
| Baseline mean (SD), mmol/L | 0.71 (0.10) | 0.71 (0.11) | 0.66 (0.05) | 0.66 (0.05) | 0.84 (0.08) | 0.84 (0.09) |
| Week 24 mean (SD), mmol/L | 0.69 (0.08) | 0.70 (0.09) | 0.77 (0.08) | 0.82 (0.08) | 0.87 (0.08) | 0.87 (0.08) |
| Adjusted change from baseline, mean (95% CI) | 0.05 | 0.05 | 0.05 | 0.05 | 0.01 | 0.01 |
| Difference vs. placebo (95% CI) | (0.01, 0.00) | (0.05, 0.06) | (0.04, 0.06) | (0.12, 0.13) | (0.02, 0.01) | (0.04, 0.04) |

CI, confidence interval; Mg, magnesium; N#, number of randomized patients with nonmissing baseline and week 24 values; SD, standard deviation.; T2D, type 2 diabetes.

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week 24 LOCF values; X, number of responders.

observation-carried-forward; Mg, magnesium; N#, number of randomized patients with level increased to patients with baseline hypomagnesemia (dapagliflozin 10 mg once daily at week 24 (LOCF). CI, confidence interval; LOCF, last-observation-carried-forward; Mg, magnesium; N#, number of randomized patients with week 24 LOCF values; X, number of responders.

Our results are consistent with recently published data on SGLT2i treatment and serum Mg.19,20 A meta-analysis reported mean increases of 0.1, 0.09, 0.07, and 0.05 mmol/L in serum Mg with dapagliflozin 10 mg, canagliflozin 300 mg, empagliflozin 25 mg, and ipragliflozin 50 mg treatment, respectively.19 Similarly, a post hoc analysis of 26-week canagliflozin treatment reported mean increases of 0.11 and 0.12 mmol/L in serum Mg with canagliflozin 100 and 300 mg treatment, respectively, in patients with T2D and hypomagnesemia.20 The results from this study are consistent with an SGLT2i class effect.19–22 Possible mechanisms underpinning this include increases in glucagon levels,42 leading to increases in Mg absorption in the distal convoluted tubule,20,22 decreases in insulin levels causing movement of intracellular Mg to the extracellular volume,22,41 small increases in serum Mg due to hemocconcentration,22 reduced Mg excretion through transient receptor potential ion channel 6,20,22 and reductions in insulin resistance leading to decreases in renal Mg wasting.22

Due to the intrinsic role of Mg in human physiology, reduced serum Mg may be implicated in the etiology of multiple diseases. There is an inverse relation between dietary Mg intake and the risk of developing T2D,44 and Mg supplementation has beneficial effects on blood glucose, insulin resistance, lipid profile, and BP in patients with T2D.5,45,46 However, the effects of Mg supplementation on other aspects of T2D pathophysiology, along with the potential effect on T2D progression, remain poorly understood.

Serum Mg is inversely and independently associated with the risk of heart failure.37,38 and Mg depletion may worsen cardiac contractility, increase vasoconstriction, and deplete cardiac energy stores in patients with heart failure.2 Hypomagnesemia in patients with heart failure is associated with complex ventricular arrhythmias that can be alleviated by Mg supplementation.26 Additionally, increasing serum Mg concentrations has been shown to lower mean arterial pressure; systolic vascular resistance; and the frequency of isolated premature ventricular complexes, couples, and nonsustained ventricular tachyarrhythmia in patients with stable congestive heart failure secondary to coronary artery disease.47

The kidneys play a crucial role in Mg homeostasis.48 In advanced chronic kidney disease, the fraction of filtered Mg excreted increases as a result of the impaired tubular reabsorption.48 Accordingly, hypomagnesemia is frequently observed in patients with chronic kidney disease/ESKD48 and is a risk factor for the nonrecovery of kidney function.49 Moreover, Mg depletion is associated with vascular pathology, cardiovascular disease, and all-cause mortality in patients with chronic kidney disease.45,50 However, there remains a lack of interventional studies that have assessed the risk-benefit of Mg supplementation in patients with chronic kidney disease.50

Results from a recent meta-analysis suggest that SGLT2i treatment reduces the risks of major adverse cardiovascular events (i.e., cardiovascular death, myocardial infarction, stroke) in patients with T2D and established atherosclerotic cardiovascular disease.14 However, more prominent benefits of SGLT2i treatment appear to be related to reducing hospitalization for heart failure and decreasing the progression of kidney disease in patients with T2D.14,16 Future prospective studies are needed to explore whether correction of hypomagnesemia directly or indirectly contributes to a reduction in the risk of cardiovascular disease or progression of chronic kidney disease.

This study has several strengths. Whilst previous studies have assessed the effects of various SGLT2i on serum Mg,19,20 this study is a novel addition to the literature as it is the first to have specifically evaluated the effect of dapagliflozin on serum Mg in patients with T2D. This allowed us to pool more clinical trials of dapagliflozin than previous studies,18 and assemble a sizeable sample of patients in order to examine effects in highly relevant subgroups. Moreover, we had multiple measures of serum Mg over an extended period using a uniform dose of dapagliflozin, and, owing to inclusion of studies in multiple geographies, representative trial participants from diverse populations.

There were several important limitations. First, the trials were not designed to examine the effects of dapagliflozin on serum Mg concentrations. Second, although the dose of dapagliflozin was uniform across studies, treatment regimens were heterogeneous (e.g., monotherapy and combination therapy with other agents); Third, there were no efforts to control dietary intake of Mg, the use of Mg supplements, or the use of Mg-containing antacids or cathartics, some of which are available over-the-counter. Fourth, although we collected information on concomitant medications, including diuretics that might augment (thiazide, thiazide-type, and loop diuretics) or diminish (mineralocorticoid antagonists, amiloride) urinary Mg excretion, we did not collect timed or spot urine collections to determine urinary Mg excretion. Fifth, we did not collect information on outcomes that might influence serum Mg concentrations (e.g., secondary hyperparathyroidism, alcohol intake, diarrhea), and these were therefore not adjusted for in the
analyses. Finally, patient ethnicity was not recorded, and, therefore, generalizations to ethnic groups should be made with caution.

In conclusion, treatment with dapagliflozin 10 mg resulted in correction of serum Mg concentration in patients with T2D and hypomagnesemia, without increased risk for hypermagnesemia. Whether the reduction in the risk of cardiovascular and renal events induced by SGLT2 inhibition is mediated in part by effects on serum Mg balance remains to be determined.

Declaration of Competing Interest

RDT is a consultant for Amgen, AstraZeneca, Boehringer Ingelheim, Quintiles, Quest Diagnostics, Relypsa, and Reata Pharmaceuticals. RG has been an advisory board member for Amgen, Abbott, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Merck, Novo Nordisk, Sanofi, Takeda, and Valeant; a research investigator for AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Merck, Novo Nordisk, Sanofi, and Takeda; and a speaker for Amgen, Abbott, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Merck, Mylan, Novo Nordisk, Sanofi, Servier, and Valeant. GMC has served as a consultant to Akebia, AMAG, Amgen, Ardelyx, AstraZeneca, Baxter, CloudCath, Cricket Health, Durect, Gilead, Goldfinch Bio, Outset Medical, Reata, and Sanofi. VC is a former employee of AstraZeneca and owns AstraZeneca stock. CDS, BVS, and PS are employees and shareholders of AstraZeneca.

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Data availability

Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca’s data sharing policy described at https://astrazenecagrouptrials.pharmcm.com/ST/Submission/Disclosure.
The studies included in this analysis were conducted according to the guidelines laid down in the Declaration of Helsinki and were approved by the respective Institutional Review Boards. All participants provided written informed consent.

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This study was funded by AstraZeneca. The sponsor was involved in the study design; collection, analysis, and interpretation of data; report writing; and the decision to submit the article for publication.

**Author contributions**

RDT, RG, GMC, VC, CDS, BVS, and PS made substantial contributions to the conception and design of the study, acquisition of data or analysis and interpretation of data; drafted the article and revised it critically for important intellectual content; and gave final approval to the version submitted for publication.

**Appendix A. Supplementary data**

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jdiacomp.2019.06.007.

**References**


