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Original Research Article

Effect of Dapagliflozin on Serum calcium, Serum phosphate and Intact Parathyroid Hormone in Patients with Diabetic Nephropathy with CKD Stage 3

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Abstract: ***Background:*** Chronic kidney disease (CKD) secondary to diabetic nephropathy is linked with CKD–mineral and bone disorder, and sodium–glucose cotransporter-2 (SGLT2) inhibitors may alter phosphate–calcium–PTH physiology. ***Aim:*** To evaluate short-term changes in serum phosphate, serum calcium, and intact parathyroid hormone (iPTH) after initiating dapagliflozin in patients with at stage 3 of CKD due to diabetic nephropathy. ***Materials and Methods***: This is a quasi-experimental study. It was carried out in the Department of Nephrology, Shaikh Zayed Hospital, Lahore from July 2025 to December 2025. Adults with type 2 diabetes and CKD stage 3 (eGFR 30–60 mL/min/1.73 m²) were enrolled consecutively (n = 71). All participants received dapagliflozin 10 mg once daily for 6 weeks. Serum phosphate, calcium, and iPTH were measured at baseline and at 6 weeks, and within-participant differences were assessed using paired statistical testing. ***Results:*** Participants had a mean age of 55 years and approximately half were male. Over 6 weeks of dapagliflozin therapy, serum phosphate increased significantly, serum calcium showed a small but significant rise, and iPTH demonstrated the most pronounced increase from baseline. All primary outcomes changed significantly at 6 weeks ($p < 0.001$). ***Conclusions:*** In CKD stage 3 diabetic nephropathy, dapagliflozin was associated with significant short-term increases in serum phosphate and iPTH, with a modest rise in serum calcium. Routine monitoring of mineral metabolism markers may be warranted after initiation.

Keywords: Chronic kidney disease; Dapagliflozin; Diabetic nephropathy; Parathyroid hormone; Serum phosphate.

INTRODUCTION

Diabetes mellitus is a rapidly expanding global health problem and a major driver of chronic kidney disease (CKD). In the most recent pooled global analysis (1990–2022), an estimated 828 million adults were living with diabetes in 2022, with the largest increases occurring in low- and middle-income countries, including South Asia [1]. CKD affects >10% of the world's population (over 800 million people), and diabetes is one of its leading risk factors, accelerating kidney function decline and increasing morbidity due to cardiovascular diseases

[2]. In patients suffering from nephropathy due to diabetes (including CKD stage 3), disturbances in mineral metabolism, particularly changes in serum phosphate, serum calcium, and parathyroid hormone (PTH), are clinically important because they relate to CKD-mineral and bone disorder (CKD-MBD), risk of vascular calcification, and long-term outcomes [2]. Over the last decade, management of diabetic kidney disease has shifted from glucose-centric therapy to organ-protective strategies. Contemporary guidance recommends early use of SGLT2 inhibitors (with foundational CKD care) because of consistent kidney and cardiovascular benefits across CKD risk strata [3]. A major milestone was the EMPA-KIDNEY trial, which demonstrated that empagliflozin reduced the risk of kidney disease progression or cardiovascular death in a broad CKD population [4]. At the same time, mechanistic and clinical studies have highlighted a "trade-off" area that remains incompletely characterized: SGLT2 inhibition can transiently raise serum phosphate and PTH (and related markers such as FGF-23), likely via altered proximal tubular sodium–phosphate handling [5]. These changes may be short-lived and clinically modest in many patients, but the evidence is not uniform across CKD stages, baseline mineral status, and comorbidity burden, leaving uncertainty about the real-world clinical significance in diabetic nephropathy [5–6].

In Pakistan, the burden is particularly concerning because both diabetes and CKD are common and frequently underdiagnosed. A recent systematic review and meta-analysis estimated a pooled prevalence of type 2 diabetes ~10% and pre-diabetes ~11% in Pakistan, translating into a very large at-risk population [7]. Local screening data from urban Lahore (high-risk adults) reported CKD in about one-fourth of participants, with significant associations with diabetes and hypertension, two dominant drivers of CKD progression and complications [8]. In this context, understanding how widely used kidney-protective therapies (such as dapagliflozin) influence clinically relevant biochemical outcomes is directly relevant to local nephrology practice [7–8].

Therefore, the present study was designed to evaluate the effect of dapagliflozin on serum serum phosphate, serum calcium, and intact parathyroid hormone (iPTH) in patients with diabetic nephropathy with CKD stage 3. The rationale is that, while SGLT2 inhibitors are now recommended for renal protection [3], their impact on mineral metabolism markers in CKD, especially in South Asian populations where CKD-MBD risk factors may differ, needs clearer characterization [5–6]. By quantifying baseline values and short-term changes after therapy, this work aims to provide clinically actionable evidence on whether dapagliflozin use is associated with meaningful shifts in serum phosphate, serum calcium, PTH homeostasis, supporting safer prescribing and better biochemical monitoring strategies in Pakistani CKD clinics [3–8].

MATERIALS AND METHODS

This was a quasi-experimental study. It was done in the Nephrology Department, Shaikh Zayed Hospital, Lahore. The duration of the study was from July 2025 to December 2025. Ethical approval was obtained from the IRRAB (Institutional Review & Research Advisory Board), TERC (Technical & Ethical Review Committee), Shaikh Zayed Medical Complex, Lahore (TERC ID: TERC/SC/INT/2025/396; approval date: 11 July 2025). Written informed consent was obtained from all participants prior to enrollment. The study duration was six months after approval of the synopsis. The sample size was 71 patients. It was calculated using the WHO sample size calculator, keeping a 15% expected change of intact parathyroid hormone levels in diabetic patients taking dapagliflozin [10], 8% absolute precision, and 95% confidence interval. Patients were recruited by non-probability consecutive sampling.

Inclusion criteria: Adults with type 2 diabetes and diabetic nephropathy were included. Age range was >18 to <75 years. Both males and females were included. Only patients with CKD stage 3 were enrolled. This was defined as eGFR 30–60 mL/min/1.73 m², calculated by the CKD-EPI formula.

Exclusion criteria: Patients were excluded if they had hypertension or had a cardiovascular event in the last 6 months. Patients were also excluded if they were using pioglitazone, GLP-1 analogues, DPP-4 inhibitors, or any SGLT-2 inhibitor. Pregnant or breastfeeding women were excluded.

Baseline information was recorded on a pre-designed proforma. It included age, gender, duration of diabetes, fasting HbA1c, and BMI. Baseline blood tests were noted for serum serum phosphate, serum calcium, and intact parathyroid hormone (iPTH). All enrolled patients received dapagliflozin 10 mg once daily for six consecutive weeks. Compliance was ensured by regular telephone contact. After six weeks, serum phosphate, serum calcium, and iPTH were measured again. The percentage change for each outcome was calculated using the formula: [(post − pre) / pre] × 100. All information was recorded on the same proforma for final compilation. IBM SPSS Statistics was used to analyse data (version 27.0). Numerical variables (age, height, weight, BMI, duration of diabetes, HbA1c, serum phosphate, serum calcium, iPTH, and percentage change) were summarized as mean ± SD. Categorical variables (such as gender) were

summarized as frequency and percentage.

For the main outcomes, baseline and 6-week values were compared within the same participants. If paired differences were approximately normal, a paired sample t-test was applied. If paired differences were not normal, a Wilcoxon signed-rank test was used. The 95% confidence interval for the mean change was reported for the primary outcomes. Data were also stratified by age, sex, duration of diabetes, HbA1c, and BMI to explore subgroup patterns. A p-value ≤ 0.05 was considered significant statistically.

RESULTS

71 participants were included in the study. The mean age was 55.2 ± 11.3 years, with an almost equal sex distribution (36 males, 50.7%; 35 females, 49.3%). The mean duration of diabetes was 10.5 ± 6.2 years. Participants had mean height 164.1 ± 8.9 cm, weight 75.8 ± 13.5 kg, and BMI 28.1 ± 4.3 kg/m², while mean HbA1c was 8.1 ± 0.8%. At baseline, mean serum phosphate was 3.67 ± 0.29 mg/dL, serum calcium was 9.09 ± 0.32 mg/dL, and intact PTH was 69.47 ± 15 pg/mL (table 1).

Among 71 participants, serum phosphate increased at 6 weeks compared with baseline, showing a statistically significant rise. Serum calcium also increased over the same period, although the magnitude of change was modest. iPTH demonstrated the largest change, with a clear increase from baseline to 6 weeks, and this difference was highly significant. Overall, the most pronounced effect over 6 weeks was observed in iPTH, followed by phosphate, while calcium showed only a small upward shift (table 2).

After 6 weeks, serum phosphate levels were largely unchanged compared with baseline, suggesting no meaningful effect on phosphate over the short follow-up period. Serum calcium showed a modest but consistent rise. In contrast, iPTH increased noticeably from baseline to 6 weeks, representing the most prominent change among the measured mineral metabolism markers (figure 1).

TABLES:

Table 1. Study participants baseline characteristics (n = 71)

Characteristic	Value
Age (years)	55.2 ± 11.3
Sex, n (%)	
Male	36 (50.7%)
Female	35 (49.3%)
Duration of diabetes (years)	10.5 ± 6.2
Height (cm)	164.1 ± 8.9
Weight (kg)	75.8 ± 13.5
BMI (kg/m²)	28.1 ± 4.3
HbA1c (%)	8.1 ± 0.8
Serum phosphate (mg/dL)	3.67 ± 0.29
Serum calcium (mg/dL)	9.09 ± 0.32
Intact PTH (pg/mL)	69.47 ± 15

Values are mean ± SD unless otherwise stated.

Table 2. Primary outcomes at baseline vs 6 weeks (n = 71)

Outcome	Baseline	6 weeks	Mean change (Δ)	Mean %Δ	p-value
Serum phosphate (mg/dL)	3.67 ± 0.29	4.04 ± 0.10	0.37	10.8	<0.001
Serum calcium (mg/dL)	9.09 ± 0.32	9.22 ± 0.32	0.14	1.5	<0.001
iPTH (pg/mL)	69.47 ± 15	81.75 ± 1.06	12.28	17.7	<0.001

Values are mean ± SD. Change (Δ) = 6 weeks − baseline. p-values from paired t-test.

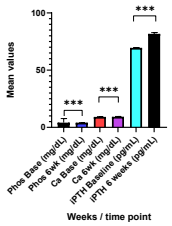

Figure 1: Mean (± SD) serum phosphate and calcium concentrations and intact parathyroid hormone (iPTH) levels at baseline and after 6 weeks of dapagliflozin therapy. *** $p < 0.001$.

DISCUSSION

In this study, dapagliflozin produced clear changes in CKD-MBD markers over 6 weeks. Serum phosphate increased from baseline to 6 weeks, and the change was significant statistically ($p<0.001$). Serum serum calcium also displayed a little but rise was significant ($p<0.001$). Intact PTH increased markedly during follow-up, and this change was highly significant ($p<0.001$). These results suggest that early mineral-hormone shifts can occur soon after starting SGLT2 inhibition in CKD stage 3 diabetic nephropathy.

These findings are biologically plausible. SGLT2 inhibition changes sodium handling in the proximal tubule. This can indirectly increase serum phosphate reabsorption through sodium–phosphate co-transport. A rise in serum phosphate can stimulate the FGF23–vitamin D–PTH axis. This can lead to higher PTH levels and measurable changes in serum calcium balance. Similar short-term electrolyte and kidney-related shifts have been reported with dapagliflozin use in local Pakistani clinical settings, showing that biochemical changes can appear early after initiation, even when the drug is generally well tolerated [9].

When compared with other studies, our pattern fits the broader literature but the direction and magnitude may vary by population and CKD severity. A large network meta-analysis of randomized trials showed that SGLT2 inhibitors can increase serum phosphate, supporting a class effect, although the average rise is usually small across diverse trials [10]. A 2024 prospective observational study in diabetic kidney disease also showed that dapagliflozin can change bone-mineral related biomarkers over short follow-up, confirming that early shifts in this pathway are possible in DKD cohorts [11]. In addition, a 2024 meta-analysis focused on bone metabolism markers reported a significant rise in PTH with SGLT2 inhibitors overall, which supports our observation of increased iPTH and suggests that this may be a reproducible signal in the short term [12]. Differences across studies can be due to baseline vitamin D status, diet, CKD stage, assay variation, follow-up duration, and use of concurrent therapies that affect CKD-MBD.

CONCLUSION

Dapagliflozin use for 6 weeks in CKD stage 3 diabetic nephropathy was associated with significant increases in serum phosphate and iPTH. Serum calcium also rose, but the change was modest compared with iPTH and phosphate. These findings support monitoring mineral metabolism parameters soon after starting SGLT2 inhibitor therapy.

LIMITATIONS OF THE STUDY

This was a short follow-up study. It cannot tell if the changes persist or stabilize later [13]. Dietary serum phosphate intake and vitamin D supplementation were not fully controlled [14]. FGF23 and vitamin D metabolites were not measured, so the mechanistic pathway cannot be confirmed directly [15]. The sample was from a single setting, so generalizability may be limited.

FUTURE DIRECTIONS

Longer follow-up is needed to see if serum phosphate and iPTH return toward baseline or remain elevated [16]. Future studies should measure 1,25-(OH), vitamin D, 25-OH vitamin D, FGF23, and 1,25-$(OH)_2$ alongside serum phosphate, serum calcium, and iPTH [17]. Subgroup analyses by CKD stage, baseline iPTH, and vitamin D status should be planned. Comparative studies with other SGLT2 inhibitors can also clarify if this is a consistent class effect in CKD stage 3 diabetic nephropathy

INTEREST CONFLICT
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CONTRIBUTION OF AUTHORS:

MUMB: Analysis design, data collection, performance of statistical analysis, paper writing, and drafted the manuscript.
MA: Conceived the analysis, supervised the study, and contributed to manuscript development.
SS: Assisted in data collection, data interpretation, and contributed to manuscript drafting.
SSC: Assisted in patient recruitment, data collection, and contributed to literature review.
HF: Contributed to data collection, laboratory coordination, and manuscript preparation.
SA: Assisted in data entry, statistical support, and manuscript formatting.
All authors approved the final version of the manuscript to be published.

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