The Association of Vitamin D Status and Vitamin D Replacement Therapy with Glycemic Control, Serum Uric Acid Levels, and Microalbuminuria in Patients with Type 2 Diabetes and Chronic Kidney Disease

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Abstract
Objective: To evaluate the relationship of vitamin D status and vitamin D replacement therapy with glycemic control, serum uric acid (SUA) levels, and microalbuminuria (MAU) in patients with type 2 diabetes (T2DM) and chronic kidney disease (CKD). Subjects and Methods: A total of 1,463 patients with T2DM and CKD (aged 14–88 years), 927 females and 536 males, were included in this study. The serum data of 25-hydroxyvitamin D, i.e., 25(OH)D, level, SUA, hemoglobin (Hb) A1c, creatinine, estimated glomerular filtration rate, and urine albumin-to-creatinine ratio (UACR) were obtained from the medical records. The Mann-Whitney U test, the χ² test, the Mantel-Haenszel test, and linear regression models were used for data analysis. Results: Vitamin D deficiency and insufficiency were evident in 770 (52.0%) and 357 (24.0%) patients, respectively. Median HbA1c levels (7.3 [IQR 3.9] vs. 6.5 [IQR 2.3]%; p < 0.01) were significantly higher in patients deficient in vitamin D than in those with a normal vitamin D status. A significantly low level of vitamin D was noted with a high UACR (β −0.01; 95% CI −0.01 to −0.001; p = 0.017) and HbA1c (β −1.1; 95% CI −1.6 to −0.6; p < 0.001), but with low levels of SUA (β 1.3; 95% CI 0.5–2.2; p = 0.002). Vitamin D replacement was associated with a significantly low level of HbA1c (7.4 [2.7] vs. 6.7 [1.9]%; p < 0.001). Conclusion: In this study, there was a high prevalence of hypovitaminosis D among T2DM patients with CKD, with a higher UACR, higher HbA1c, and lower SUA being noted as playing a role in predicting a decrease in vitamin D levels and potential benefits of vitamin D replacement therapy on glycemic control in T2DM management.

Introduction
In calcium-phosphate homeostasis and bone physiology, it is well known that vitamin D status is associated with a number of nonskeletal functions including glucose homeostasis, pathophysiology, and the progression of type 2 diabetes mellitus (T2DM) [1–3]. The serum 25-hydroxyvitamin D, i.e., 25(OH)D, level is considered to be the most stable and reliable indicator of vitamin D status [4, 5]. It reflects vitamin D exposure based on the sum of endogenous synthesis and dietary intake from foods, for-
tified products, and/or supplements [4, 5]. Most patients with T2DM have low 25(OH)D levels, while high levels are associated with a lower risk of incident diabetes [6, 7]. Reduced nephron mass and/or 1-α hydroxylase enzyme activity has been shown to be associated with a decline in 1.25 dihydroxyvitamin D, i.e., 1.25(OH)2D, levels in patients with chronic kidney disease (CKD) [8]. Hence, it has been suggested that renal status be considered in studies involving vitamin D status among T2DM patients [7].

Serum uric acid (SUA) has been shown to be associated with reduced levels of 1.25(OH)2D via the inhibition of 1-α hydroxylase activity [9, 10] as well as with microalbuminuria (MAU) [11]. This seems notable, since MAU is considered to be a biomarker for diagnosing diabetic kidney disease, and is a predictive factor for the progression to end-stage renal disease (ESRD) and increased cardiovascular risk among diabetic patients [12, 13].

Vitamin D supplementation for diabetic patients is of particular interest, with regard to its role in glucose homeostasis and thus its use as a potential cost-effective adjunct therapy in T2DM management [14, 15]. However, data on the impact of maintaining an adequate vitamin D status or supplementing with vitamin D on clinical outcomes in diabetic patients are inconsistent, probably reflecting the differences across studies in baseline vitamin D levels and replacement therapy dosage [14–16]. This study was therefore designed to evaluate the relationship of vitamin D status and vitamin D replacement therapy with glycemic control, SUA levels, and MAU in patients with T2DM and CKD.

**Subjects and Methods**

**Study Population**

A total of 1,463 patients with T2DM and CKD (age range 14–88 years), 927 females and 536 males, who had their serum 25(OH)D levels measured during follow-up at our diabetes outpatient clinic between January 2010 and January 2015, were included in this retrospective study. Exclusion criteria were an age of <18 years, pregnancy, a change in antidiabetic treatment during the study, and no data on concomitantly assessed vitamin D levels.

The study was conducted in full accordance with the local Good Clinical Practice guideline and current legislation, and permission was obtained from the Institutional Ethics Committee for the use of patient data for publication purposes.

**Study Assessments**

Data on patient demographics, laboratory parameters including analysis for 25(OH)D, SUA, HbA1c, creatinine, estimated glomerular filtration rate (eGFR), and urine albumin-to-creatinine ratio (UACR) were obtained from medical records. Demographic characteristics and laboratory parameters were evaluated with respect to vitamin D status, while estimators of baseline vitamin D levels and the effect of vitamin D replacement therapy on the vitamin D, glycemic, and renal function parameters were also analyzed. Overall, 383 of 1,463 patients received vitamin D replacement therapy (75,000 units weekly). Pretreatment and posttreatment laboratory parameters were compared in these patients.

**Blood Biochemistry Analysis**

25(OH)D, creatinine, uric acid, HbA1c, and hemoglobin were measured using a central laboratory biochemistry analyzer (ICT [ISE] Module of ARCHITECT c16000, Abbott Laboratories, Abbott Park, IL, USA). 25(OH)D levels were measured using high-performance liquid chromatography, and were classified as deficient (<20 ng/mL), insufficient (20–30 ng/mL) or optimal (>30 ng/mL) [17].

**Estimation of the Glomerular Filtration Rate**

The GFR was estimated according to the Modification of Diet in Renal Disease (MDRD) equation, which includes 4 variables: eGFR (mL/min/1.73 m²) = 175 × (serum creatinine)−0.203 × (age)−0.0203 × (0.742 if female) (conventional units) [18]. The patients were then classified into 5 CKD stages: stage 1 (eGFR >90 mL/min/1.73 m²); stage 2, mild CKD (eGFR 60–89 mL/min/1.73 m²); stage 3, moderate CKD (eGFR 30–59 mL/min/1.73 m²); stage 4, severe CKD (eGFR 15–29 mL/min/1.73 m²); and stage 5, end-stage CKD (eGFR <15 mL/min/1.73 m²).

**Statistical Analysis**

Categorical variables were summarized as n (%) and continuous variables as median (IQR) due to non-normal distribution patterns. Baseline vitamin D level groups were compared by means of the Mann-Whitney U test for continuous variables, the χ² test for nominal variables, and the Mantel-Haenszel test for ordinal variables. The estimators of baseline vitamin D levels were evaluated by using univariate and multivariate (adjusted for age and gender) linear regression models. The effect of vitamin D replacement therapy during follow-up was evaluated by the Wilcoxon or McNemar-Bowker test depending on the variables. Type 1 error level was set at 5% and the Bonferroni adjustment for a type 1 error was used, where appropriate. Statistical analysis was conducted with Statistical Package for the Social Sciences software (v21.0, released 2012, IBM Corp., Armonk, NY, USA).

**Results**

**Demographic Characteristics and Laboratory Findings**

The median (IQR) 25(OH)D level was 18.1 (15.5) ng/mL; vitamin D deficiency and insufficiency were evident in 770 (52.6%) and 357 (24.4%) patients, respectively. Stage 1–2 CKD was noted in 1,308 (91.9%) patients. The median (IQR) level of HbA1c was 7.0 (3.9%) and that of uric acid was 4.9 (1.9) mg/dL in the overall study population (Table 1).

Vitamin D deficiency was associated with a significantly higher number of females (n = 527; 68.4% vs. n = 197; 58.6%; p = 0.003) and higher (median [IQR]) HbA1c.
levels (7.3 [3.2] vs. 6.5 [2.3]%; p < 0.01) compared with normal vitamin D status. Patients with vitamin D deficiency and insufficiency had significantly lower levels for SUA (4.7 [2.0] and 4.7 [1.7] vs. 5.1 [1.9] mg/dL, respectively; p < 0.001 for each), and higher UACR (14.9 [42.9] and 15.2 [41.7] vs. 9.5 [19.6] mg/mmol; p < 0.01 for each) when compared to patients with a normal vitamin D status (Table 1).

### Estimators of Baseline Vitamin D Levels

Univariate linear regression analyses revealed lower vitamin D levels with higher UACR (β = −0.01; 95% CI −0.01 to −0.001; p = 0.017) and HbA1c (β = −1.1; 95% CI −1.6 to −0.6; p < 0.001) levels but lower SUA (β = 1.3; 95% CI 0.5–2.2; p = 0.002), even after adjusting for age and gender (p = 0.023, p = 0.013, and p < 0.001, respectively; Table 2).

### Effect of Vitamin D Replacement Therapy on Laboratory Findings

Among patients who had vitamin D replacement therapy (n = 383), after a median (IQR) 6.0 (5.0) months, there was a significant increase in (median [IQR]) 25(OH)D levels (from 18.1 [15.5] ng/mL pretreatment to 25.5 [19.1] ng/mL posttreatment; p < 0.001) and the percentage of patients with normal vitamin D status (from 19.8 to 37.1%; p < 0.001) (Table 3). When compared to pretreatment values, posttreatment values showed a significant decrease (median [IQR]) in HbA1c (7.4 [2.7] vs. 6.7 [1.9]%; p < 0.001) and eGFR (92.3 [30.3] vs. 91.4 [30.4] mL/min/1.73 m²; p < 0.001). Analysis of data adjusted for follow-up duration also revealed a significant decrease in mean (95% CI) HbA1c levels from baseline to follow-up (7.8 [7.6–8.0] vs. 7.1 [6.9–7.2]%; p < 0.001) (Table 3).

### Discussion

Our findings in a cohort of patients with T2DM and CKD revealed a high prevalence (approx. 70%) of hypovitaminosis D, particularly among females, in cases of vitamin D deficiency. Higher levels of HbA1c and UACR,
and lower levels of SUA were shown to predict lower vitamin D levels. Vitamin D replacement revealed an increase in patients with normal vitamin D status, along with a significant decrease in HbA1c levels.

The high 76.0% prevalence of hypovitaminosis D in our cohort, particularly among females, in cases of vitamin D deficiency, was similar to the previously published data indicating, overall, a 73.0% prevalence of hypovitaminosis D (higher in females) among Turkish T2DM patients [19, 20].

This lower level of 25(OH)D among diabetic patients and higher HbA1c in cases of hypovitaminosis D than with vitamin D sufficiency was also reported in other studies on diabetic patients with various stages of CKD [7, 19, 21, 22]. Our findings also revealed a significant role of higher HbA1c in predicting a decrease in vitamin D levels, in agreement with previous studies [7, 23, 24].

### Table 2. Estimators of baseline vitamin D levels

| Parameters                  | Univariate | p value | Adjusted* | p value |
|-----------------------------|------------|---------|-----------|---------|
| Serum creatinine, mg/dL     | 1.3 (–2.9 to 5.5) | 0.541 | –1.2 (–5.9 to 3.6) | 0.629 |
| eGFR, mL/min/1.73 m²        | –0.03 (–0.07 to 0.02) | 0.212 | –0.02 (–0.07 to 0.03) | 0.372 |
| UACR, mg/mmol               | –0.01 (–0.01 to –0.001) | 0.017 | –0.01 (–0.01 to –0.001) | 0.023 |
| SUA, mg/dL                  | 1.3 (0.5–2.2) | 0.002 | 1.1 (0.2–2.0) | 0.013 |
| HbA1c, %                    | –1.1 (–1.6 to –0.6) | <0.001 | –1.2 (–1.7 to –0.8) | <0.001 |

Data on some patients are missing, so the results are based on the available data. β, linear regression coefficient; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin A1c; SUA, serum uric acid; UACR, urine albumin-to-creatinine ratio.

* Results of linear regression model which was adjusted for patients’ age and gender.

### Table 3. Effect of vitamin D replacement therapy on renal function and glycemic parameters and vitamin D status

| Parameters                  | Patients, n | At baseline | After treatment | p valuea |
|-----------------------------|-------------|-------------|----------------|---------|
| **Renal function**          |             |             |                |         |
| Serum vitamin D, ng/mL      | 383         | 18.1 (15.5) | 25.5 (19.1)    | <0.001  |
| Serum creatinine, mg/dL     | 368         | 0.8 (0.2)   | 0.8 (0.2)      | 0.054   |
| eGFR, mL/min/1.73 m²        | 368         | 92.3 (30.3) | 91.4 (30.4)    | <0.001  |
| SUA, mg/dL                  | 72          | 4.8 (2.0)   | 5.0 (1.5)      | 0.470   |
| **HbA1c, %b**               | 373         | 7.4 (2.7)   | 6.7 (1.9)      | <0.001  |
| Mean (95% CI)               | 7.8 (7.6–8.0) | 7.1 (6.9–7.2) | <0.001  |
| **Vitamin D status, n (%)** |             |             |                |         |
| Deficiency                  | 224 (58.5)  | 140 (36.6)  | <0.001         |
| Insufficiency               | 83 (21.7)   | 101 (26.4)  |               |
| Normal                      | 76 (19.8)   | 142 (37.1)  |               |

eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin A1c; SUA, serum uric acid; UACR, urine albumin-to-creatinine ratio.

a Results of comparison to normal vitamin D group.

b Median (IQR).
In this cohort, the increase in median 25(OH)D level, from 18.1 to 25.5 ng/mL, along with an increase in the rate of normal vitamin D status, from 19.8 to 37.1%, due to the vitamin D replacement, could have produced extraskel-etal benefits of vitamin D as suggested previously [25].

The significant improvement in HbA1c levels after vitamin D replacement therapy that we observed empha-
sizes the association of vitamin D levels with glucose he-
mostasis in T2DM, and the potential therapeutic implica-
tions of this association in achieving improved glycemic control in T2DM management [21]. Similar to our find-
ings, the likely benefit of vitamin D substitution for a bet-
ter T2DM prognosis was suggested in a 15-year longitu-
dinal study among T2DM patients [26]. Clinical trials, however, have revealed inconsistent findings on the im-
 pact of maintaining adequate vitamin D status and/or high-dose vitamin replacement on long-term glycemic control in T2DM patients [14–16, 27]. Thus, the need for validation by further large-scale, cross-sectional, and intervention clinical studies is emphasized [15].

Given that renal status is a covariant influencing vita-
m D status [7], it seems worth noting that the majority of our patients had stage 1–2 CKD and no difference was noted in the CKD stage of the patients with respect to vitamin D status.

A decrease in SUA was amongst the predictors of hy-
povitaminosis D in our study. This seems to contrast with past studies that indicated an association between hyper-
uricemia and hypovitaminosis D in gout, diabetes, and CKD patient populations [10, 19, 28]. In addition, no as-
 sociation was shown between reduced 25(OH)D levels and elevated SUA in premenopausal women, regardless of concomitant T2DM and hypertension [29]. This seems to indicate the likelihood of a multifaceted pathogenesis of the interaction between vitamin D status and SUA, with the contribution of several endocrine factors [9, 30].

In this cohort, higher UACR was shown to predict a decrease in vitamin D levels. This seems to support the linear relation between vitamin D deficiency and progress-
ion of MAU reported in T2DM patients [13, 27], while also emphasizing the potential benefit of the normaliza-
tion of vitamin D levels in the reduction of renal and car-
diovascular risks associated with MAU in these patients [12, 13].

Certain limitations to this study include its retrospec-
tive, single-center design and thus an inability to general-
ize our findings to the overall diabetic population, the lack of data on parathyroid hormone levels and seasonal changes in vitamin D levels, and also the fact that there was no standard duration of vitamin D treatment.

Conclusion

Our findings in a cohort of patients with T2DM and CKD revealed a high prevalence (70%) of hypovitaminosis D, particularly among females, in cases of vitamin D deficiency. Higher UACR, higher HbA1c, and lower SUA were shown to predict a decrease in vitamin D levels. Vi-
tamin D replacement therapy had a beneficial effect on glucose hemostasis via a significant reduction in HbA1c; this emphasizes the potential therapeutic implications of vitamin D supplementation as a promising preventative and therapeutic agent for improved glycemic control among T2DM patients with CKD. We recommend an evaluation of the relationship between hypovitaminosis D and SUA and of the impact of longer-term vitamin D replacement therapy on glycemic control and renal function among diabetic patients in a large-scale clinical study.

Disclosure Statement

There were no conflicts of interest.

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