Vitamin-D deficiency is Encountered in Almost all Egyptian Stage 3–5 Chronic Kidney Disease Patients in Spite of the Sunny Weather

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ABSTRACT. Currently, there is no available data about Vitamin D status among Egyptian chronic kidney disease (CKD) patients. This cross-sectional study is looking for the prevalence of Vitamin D deficiency among Stage 3a–5 CKD Egyptian patients and its possible associations. We studied 1624 Stage 3a–5 CKD adults (689 males and 935 females) together with 200 normal control persons. All the recruited candidates were tested for body mass index (BMI); serum levels of blood urea nitrogen, creatinine, calcium (Ca), phosphorus (P), parathyroid hormone (PTH), 25 hydroxy vitamin D (25(OH)D), albumin, and uric acid (UA); urine albumin/creatinine ratio (ACR), and estimated glomerular filtration rate. The optimal level of Vitamin D was encountered in only 1.4% of CKD patients versus 52% of the normal controls. A total of 1107 (68.2%) CKD patients versus 23 (11.5%) controls had serum 25(OH)D ≤20 ng/mL (mean ± standard deviation = 16.8 ± 5.8 versus 37.3±7.6 ng/mL for CKD versus control group, respectively, P <0.001). There was a highly statistically significant positive correlation between serum 25(OH)D and serum Ca (r = 0.299, P <0.001) and a highly statistically significant negative correlation between serum 25(OH)D on the one hand and serum P, serum PTH, serum UA, and urine ACR on the other hand (r = −0.46, −0.69, −0.73, and −0.8, respectively, P <0.001). Vitamin D deficiency is very common among Egyptian CKD patients. Serum P, UA, and urine ACR ratio are the most important variables which are found to be negatively associated with serum 25(OH)D.

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Introduction
The role of Vitamin D in bone and mineral metabolism is pivotal. Beside its central role in calcium (Ca) and phosphate metabolism, it is very essential for musculoskeletal development and health.¹ Vitamin D deficiency may
have an additional impact on different body organs. The hepatic 25-hydroxylase enzyme (CYP2R1) converts Vitamin D into 25 hydroxy vitamin D (25(OH)D). Serum 25(OH)D level reflects Vitamin D status in humans. The normal level is above 30 ng/mL, whereas a level below 20 ng/mL is considered as Vitamin D deficiency. Vitamin D deficiency may predispose to cardiovascular, neoplastic, infectious, metabolic, and autoimmune diseases. The rate of progression of chronic kidney disease (CKD) might accelerate in Vitamin D–deficient cases. CKD patients have impaired renal 1-α hydroxylase (CYP27B1) activity with consequent decrease in the rate of conversion of 25(OH)D to calcitriol. This can lead to secondary hyperparathyroidism. Superimposed deficiency of 25(OH)D may aggravate secondary hyperparathyroidism both directly and indirectly. Calcitriol level should not be used to diagnose Vitamin D deficiency as it can lead to erroneous interpretations of Vitamin D status. Calcitriol levels are usually normal or even elevated in Vitamin D–deficient patients as a result of elevated parathyroid hormone (PTH) levels.

Egypt has sunny weather all over the four seasons of the year. In spite of the sunny weather, restricted exposure to sunlight is very common mainly due to religious and cultural rules. Food fortification with Vitamin D is optional in Egypt. CKD patients have additional factors that can increase the prevalence and severity of Vitamin D deficiency. These factors include anorexia, dietary restriction, diabetes, and increased body mass index (BMI). To date, the status of Vitamin D among the Egyptian predialysis CKD patients has not been evaluated.

**Patients and Methods**

This study has recruited 1624 (688 males and 936 females) CKD patients. Their ages ranged between 18 and 55 years. The etiology of their renal disease is summarized in Table 1. A total of 271 (16.7%) patients were in Stage 3, 1290 (79.4%) were in Stage 4, and 63 (3.9%) were in Stage 5. Two hundred normal persons were included as control group. All the recruited candidates were individually interviewed for history taking and clinical examination and to obtain a written consent after discussing the mission of the study. Blood and urine samples were then collected for laboratory assessment of the different planned parameters. Intact PTH level was determined by enzyme-amplified sensiti-vity immunoassay (Roche Diagnostics, IN, USA), 25(OH)D was assessed using high-performance liquid chromatography, and estimated glomerular filtration rate (eGFR) was measured using the Modification of Diet in Renal Disease equation.

The IBM SPSS Statistics for Windows version 24.0 (IBM Corp., Armonk, NY, USA) was used for data analysis. Data were summarized as mean and standard deviation. Comparison between groups was evaluated using Student’s t-test. Correlation coefficient between different parameters of mineral metabolism and kidney function tests was also performed.

### Results

The results are summarized in Tables 1-9 and Figures 1-4. Nearly 98.6% of the CKD patients (1602) had suboptimal 25(OH)D levels (<30 ng/mL). There was no statistically significant difference in serum 25(OH)D level among CKD group based on gender (Table 3), BMI (Table 4), or on the presence or absence of diabetes mellitus (Table 5). The ratio of CKD patients with serum level of 25(OH)D less than 10 ng/mL, between 10 and 19.9

### Table 1. Etiology of chronic kidney disease.

| Etiology               | No. (%)         | Etiology               | No. (%)         |
|------------------------|-----------------|------------------------|-----------------|
| Diabetes mellitus      | 527 (32.5%)     | Systemic hypertension  | 379 (23.3%)     |
| Chronic interstitial nephritis | 287 (17.6%) | Chronic glomerulonephritis | 56 (3.4%)   |
| Obstructive uropathy   | 158 (9.8%)      | Polycystic kidney disease | 82 (5%)    |
| Reflux nephropathy     | 39 (2.4%)       | Hereditary nephropathy | 14 (0.86%)    |
| Gouty nephropathy      | 56 (3.4%)       | Urinary tract infection | 26 (1.6%)   |
ng/mL, between 20 and 29.9 ng/mL, or 30 ng/mL or more was not statistically different based on gender (Table 3), BMI (Table 4), or diabetic status (Table 5).

On the other hand, there was a statistically significant difference in serum 25(OH)D based on urine albumin excretion (10.7 ± 2.08 vs. 20.6 ± 4.15 ng/mL) in patients with increased versus normal urine albumin, respectively, \( P < 0.001 \), Table 6). A similar finding was observed in patients with serum UA >5 mg/dL versus patients with lower levels (10.9 ± 2.94 vs. 21 ± 4.35 ng/mL, respectively, \( P < 0.001 \), Table 7).

| Parameter                      | CKD group (1624) | Control group (200) | \( P \) |
|--------------------------------|------------------|---------------------|--------|
|                                | Range            | Mean ± SD           | Range  | Mean±SD |
| Age (years)                    | 18–55            | 28±8.75             | 18–54  | 29±7.06  | NS    |
| Body mass index (kg/m²)        | 17.5–30          | 23.5±2.71           | 22.5–31| 25.6±2.09| <0.01 |
| Blood urea nitrogen (mg/dL)    | 8–35             | 19±3.91             | 12–18  | 10.2±1.85| <0.001|
| Serum creatinine (mg/dL)       | 1.9–4.3          | 2.9±0.57            | 0.6–1.0| 0.8±0.09 | <0.001|
| Serum albumin (g/dL)           | 3–3.8            | 3.5±0.13            |        |         |       |
| eGFR (mL/min/1.73 m²)          | 11.4–49.3        | 22.7±6.66           | 72–104 | 88±12.3  | <0.001|
| Serum calcium (mg/dL)          | 7.5–8.8          | 8±0.28              | 8.1–9.0| 8.5±0.27 | <0.02 |
| Serum phosphorus (mg/dL)       | 3.4–5.5          | 4.3±0.64            | 3.4–4.3| 3.6±0.47 | <0.001|
| Serum PTH (pg/mL)              | 44.3–98.5        | 77.8±14.04          | 44–48.6| 45.6±1.34| <0.001|
| Serum 25(OH)D (ng/mL)          | 8–32             | 16.8±5.8            | 22.5–49.8| 37.3±7.6| <0.001|
| Serum uric acid (mg/dL)        | 3.7–7.9          | 4.9±1.13            | 4–5.1  | 4.2±0.48 | <0.001|
| Urine ACR (mg/g)               | 6.7–70.8         | 22.4±20.49          | 8–19   | 12±0.4   | <0.001|

SD: Standard deviation, CKD: Chronic kidney disease, NS: Not significant, eGFR: Estimated glomerular filtration rate; PTH: Parathyroid hormone, ACR: Albumin/creatinine ratio, 25(OH)D: 25 hydroxy vitamin D, Ca: Calcium.

Table 2. Patient versus control groups.

Table 3. Comparative analysis of different studied quantitative parameters according to gender.
Table 4. Comparative analysis of different studied quantitative parameters according to body mass index.

| Parameter                  | BMI ≥26 kg/m² (211) | BMI <26 kg/m² (1413) | P   |
|----------------------------|---------------------|----------------------|-----|
| Age (years)                | 18–55               | 18–55                | 0.93|
| BMI (kg/m²)                | 26–30               | 17.5–25.9            | <0.001|
| Blood urea nitrogen (mg/dL)| 8–35                | 8–35                 | 0.53|
| Serum albumin (g/dL)       | 1.9–4.3             | 1.9–4.3              | 0.36|
| eGFR (mL/min/1.73 m²)      | 12.2–48.3           | 22.4±6.66            | 0.35|
| Serum calcium (mg/dL)      | 7.5–8.8             | 7.5–8.8              | 0.68|
| Serum phosphorus (mg/dL)   | 3.4–5.5             | 3.4–5.5              | 0.68|
| Serum PTH (pg/mL)          | 44.3–98.5           | 77.8±14.05           | 0.54|
| Serum 25(OH)D (ng/mL)      | 8–32                | 8–32                 | 0.95|
| Serum 25(OH)D <10 ng/mL    | 26 (12.32%)         | 177 (12.53%)         | 0.7 |
| Serum 25(OH)D 10 and 19.9 ng/mL | 120 (56.87%) | 764 (54.07%)   |       |
| Serum 25(OH)D 20 and 29.9 ng/mL | 62 (29.38%) | 453 (32.06%) |       |
| Serum 25(OH)D ≥30 ng/mL    | 3 (1.44%)           | 19 (1.34%)           |       |
| No. of cases (%)           | No. of cases (%)    | No. of cases (%)     |     |

BMI: Body mass index, SD: Standard deviation, eGFR: Estimated glomerular filtration rate, PTH: Parathyroid hormone, 25(OH)D: 25 hydroxy vitamin D, ACR: Albumin/creatinine ratio.

Table 5. Comparative analysis of different studied quantitative parameters according to diabetic status.

| Parameter                  | Diabetic patients (527) | Nondiabetic patients (1097) | P   |
|----------------------------|-------------------------|-----------------------------|-----|
| Age (years)                | 18–55                   | 18–55                       | 0.31|
| Body mass index (kg/m²)    | 17.5–30                 | 17.5–30                     | 0.88|
| BUN (mg/dL)                | 10–35                   | 8–35                        | 0.01|
| Serum albumin (g/dL)       | 1.9–4.3                 | 1.9–4.3                     | 0.07|
| Serum creatinine (mg/dL)   | 3–3.8                   | 3–3.8                       | 0.62|
| eGFR (mL/min/1.73 m²)      | 11.4–48.3               | 11.9–49.3                   | 0.19|
| Serum calcium (mg/dL)      | 7.5–8.8                 | 7.5–8.8                     | 0.56|
| Serum phosphorus (mg/dL)   | 3.4–5.5                 | 3.4–5.5                     | 0.49|
| Serum PTH (pg/mL)          | 44.3–98.5               | 44.3–98.5                   | 0.92|
| Serum 25(OH)D (ng/mL)      | 8–32                    | 8.7–32                      | 0.4 |
| Serum uric acid (mg/dL)    | 3–7.9                   | 3.7–7.9                     | 0.06|
| Urine ACR (mg/g)           | 6.7–70.8                | 6.7–70.8                    | 0.23|

No. of cases (%) | No. of cases (%) | No. of cases (%) |

Serum 25(OH)D <10 ng/mL | 58 (11%) | 143 (13.04%) | 0.074 |
| Serum 25(OH)D 10 and 19.9 ng/mL | 296 (56.17%) | 589 (53.69%) |       |
| Serum 25(OH)D 20 and 29.9 ng/mL | 169 (32.07%) | 346 (31.5%) |       |
| Serum 25(OH)D ≥30 ng/mL | 4 (0.76%) | 19 (1.7%) |       |

SD: Standard deviation, BMI: Body mass index, BUN: Blood urea nitrogen; eGFR: Estimated glomerular filtration rate, PTH: Parathyroid hormone, 25(OH)D: 25 hydroxy vitamin D, ACR: Albumin/creatinine ratio.
Table 6. Comparative analysis of different studied quantitative parameters according to urine albumin excretion.

| Parameter               | UAE <30 mg/g (957) | UAE >30 mg/g (667) | P       |
|-------------------------|--------------------|--------------------|---------|
|                         | Range   | Mean±SD     | Range   | Mean±SD     |         |
| Age (years)             | 18–55   | 28±8.88     | 18–55   | 28±8.56     | NS      |
| Body mass index (kg/m²) | 17.5–30 | 23.5±2.72   | 17.5–30 | 23.5±2.71   | NS      |
| Blood urea nitrogen (mg/dL) | 8–35    | 19±3.98     | 8–35    | 19±3.82     | NS      |
| Serum creatinine (mg/dL) | 1.9–4.3 | 2.9±0.56    | 1.9–4.3 | 2.9±0.57    | NS      |
| Serum albumin (g/dL)    | 3–3.8   | 3.5±0.13    | 3–3.8   | 3.5±0.13    | NS      |
| eGFR (mL/min/1.73 m²)   | 12–49.3 | 22.8±6.58   | 11.4–47.3 | 22.6±6.78 | NS      |
| Serum calcium (mg/dL)   | 7.7–8.7 | 8.1±0.23    | 7.5–8.8 | 7.8±0.33    | <0.001  |
| Serum phosphorus (mg/dL)| 3.5–5.5 | 4.1±0.58    | 3.4–5.4 | 5±0.65     | <0.001  |
| Serum PTH (pg/mL)       | 44.3–96.8 | 70±12.02    | 70.5–98.5 | 89.4±8.3 | <0.001  |
| Serum 25(OH)D (ng/mL)   | 8–32    | 20.6±4.15   | 8.7–17  | 10.7±2.08   | <0.001  |
| Serum uric acid (mg/dL) | 3.7–5.9 | 4.7±0.58    | 4.4–7.9 | 6.8±0.95    | <0.001  |

UAE: Urine albumin excretion, eGFR: estimated glomerular filtration rate, PTH: Parathyroid hormone, ACR: albumin/creatinine ratio, NS: Nonsignificant, SD: Standard deviation, 25(OH)D: 25 hydroxy vitamin D.

Table 7. Comparative analysis of different studied quantitative parameters according to serum uric acid.

| Parameter               | SUA ≤5 mg/dL (866) | SUA >5 mg/dL (758) | P       |
|-------------------------|--------------------|--------------------|---------|
|                         | Range   | Mean±SD     | Range   | Mean±SD     |         |
| Age (years)             | 18–55   | 28±8.78     | 18–55   | 28±8.71     | NS      |
| Body mass index (kg/m²) | 17.5–30 | 23.5±2.73   | 17.5–30 | 23.5±2.69   | NS      |
| Blood urea nitrogen (mg/dL) | 8–35    | 18±4        | 8–35    | 19±3.81     | NS      |
| Serum creatinine (mg/dL) | 1.9–4.3 | 2.9±0.57    | 1.9–4.3 | 2.9±0.57    | NS      |
| Serum albumin (g/dL)    | 3–3.8   | 3.5±0.13    | 3–3.8   | 3.5±0.13    | NS      |
| eGFR (mL/min/1.73 m²)   | 11.4–49.3 | 22.8±6.63   | 11.9–47.3 | 22.5±6.71 | NS      |
| Serum calcium (mg/dL)   | 7.7–8.7 | 8±0.24      | 7.5–8.8 | 7.9±0.32    | <0.001  |
| Serum phosphorus (mg/dL)| 3.5–5.5 | 4±0.63      | 3.4–5.4 | 4±0.6      | <0.001  |
| Serum PTH (pg/mL)       | 44.3–96.8 | 69±12.15    | 69–98.5 | 88±8.73    | <0.001  |
| Serum 25(OH)D (ng/mL)   | 8–32    | 21±4.35     | 8.7–19  | 10.9±2.94   | <0.001  |
| Urine ACR (mg/g)        | 6.7–70.8 | 8.7±15.49   | 7.6–70.8 | 40.8±16.17 | <0.001  |

SUA: Serum uric acid, eGFR: estimated glomerular filtration rate, PTH: Parathyroid hormone, ACR: albumin/creatinine ratio, NS: Not significant, 25(OH)D: 25 hydroxy vitamin D.

Table 8. Correlation between different parameters and serum 25 hydroxy vitamin D.

| Parameter                          | 25(OH)D (ng/mL) | P       |
|------------------------------------|-----------------|---------|
|                                    | Correlation coefficient (r) |         |
| Age (years)                        | −0.02           | NS      |
| Body mass index (kg/m²)            | −0.01           | NS      |
| Blood urea nitrogen (mg/dL)        | −0.05           | <0.05   |
| Serum creatinine (mg/dL)           | 0.011           | NS      |
| Serum albumin (g/dL)               | 0.063           | <0.02   |
| eGFR (mL/min/1.73 m²)              | −0.01           | NS      |
| Serum Calcium (mg/dL)              | 0.299           | 0.0     |
| Serum phosphorus (mg/dL)           | −0.46           | 0.0     |
| Serum PTH (pg/mL)                  | −0.69           | 0.0     |
| Urine albumin/creatinine ratio (mg/g) | −0.8          | 0.0    |
| Serum uric acid                    | −0.73           | 0.0    |

25(OH)D: 25 hydroxy vitamin D, eGFR: Estimated glomerular filtration rate, NS: Not significant, Ca: Calcium.
Table 9. Multivariate linear regression for predictors of Vitamin D level.

| Parameter       | Coefficient | 95% CI         | P    |
|-----------------|-------------|----------------|------|
| Age             | 0.002       | -0.01 to 0.02  | 0.8  |
| BMI             | -0.02       | -0.07 to 0.03  | 0.4  |
| Serum calcium   | 1.79        | 1.05 to 2.53   | <0.0001 |
| Serum phosphorous| -2.05      | -2.38 to 1.71  | <0.0001|
| Serum PTH       | -0.10       | -0.12 to -0.09 | <0.0001|
| Urine ACR       | -0.09       | -0.11 to -0.08 | <0.0001|
| Serum uric acid | -1.59       | -1.79 to -1.39 | <0.0001|
| Serum albumin   | 0.9         | -0.15 to 2.02  | 0.09 |
| eGFR            | -0.04       | -0.06 to -0.014| 0.001|

CI: Confidence interval, BMI: Body mass index, PTH: Parathyroid hormone, ACR: Albumin/creatinine ratio, eGFR: Estimated Glomerular filtration rate.

Figure 1. Correlation between serum phosphorus and serum 25 hydroxy vitamin D.

Figure 2. Correlation between serum uric acid and serum 25 hydroxy vitamin D.
A statistically significant positive correlation (two-tailed \(P < 0.001\) if \(r \geq 0.082\)) was encountered between serum 25(OH)D and serum Ca \((r = 0.3)\) and significant negative correlations between serum 25(OH)D and serum P \((r = -0.46)\), serum PTH \((r = -0.69)\), serum UA \((r = -0.73)\), and urine albumin/creatinine ratio (ACR) \((r = -0.8)\). Age, BMI, and eGFR failed to have a significant association with serum 25(OH)D (Table 8).

**Discussion**

The central role of Vitamin D in Ca homeostasis and bone welfare is well established. To maximize the beneficial effects of Vitamin D, the serum level of 25(OH)D should be kept above 30 ng/mL\(^{10,11}\). In the current study, 98.6% of the CKD patients have serum level below this target. We failed to encounter similar alarming figure in the literature. In Louisiana, 77% of CKD patients had suboptimal levels of 25(OH)D\(^{12}\), whereas in Italy, a more sunny country compared to Louisiana, only 39.6% of the studied CKD patients were considered Vitamin D insufficient\(^{13}\). Among healthy controls, Vitamin D insufficiency is connected to inadequate sun exposure and
poor food fortification. For CKD patients, additional factors are accused as causes of increased prevalence and severity of Vitamin D insufficiency. Decreased food intake, dietary restriction, old age, increased body weight, and diabetic status were incriminated in different studies. However, the association between these different factors and serum level of 25(OH)D lacks consistency. Many studies failed to find an association between Vitamin D status on the one hand and age, BMI, urine albumin excretion, and eGFR on the other hand. In the current study, we failed to encounter significant association between Vitamin D status and any of these variables.

It seems that air pollution might interfere with sun effect. Most of the Egyptian adult females lack adequate exposure to sun thanks to culture and religious reasons. However, there was no appreciable difference in the prevalence and severity of Vitamin D deficiency between male and female Egyptian CKD patients. In addition, in Brazil, which possesses sunny weather comparable to Egypt, Vitamin D deficiency is dramatically much lower compared to Egypt (20% vs. 68.2%, respectively). It is worth mentioning that a significant difference has been also observed among healthy control persons of the current study and elsewhere with similar sunny weather.

The current study demonstrates a highly significant association between Vitamin D status and serum Ca, serum phosphorus, serum PTH, serum UA, and urine ACR. These results might suggest that different variables can have an impact on Vitamin D status in CKD. These variables are metabolic and functional consequences of CKD.

In addition, this study raised suggestions for future studies to explain the marked discrepancy in the prevalence and severity of Vitamin D deficiency that cannot be explained by the environmental and nutritional factors, the inconsistency in the association between Vitamin D deficiency, and the different factors accused in different studies beside the negative association between 25(OH)D on the one hand and serum P and serum UA on the other hand.

Ethical Committee Approval

The local ethical committee of the Internal Medicine department, School of Medicine, Cairo University, approved this work.

Human and Animal Rights

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from all the individual participants included in the study.

Conflict of interest: None declared.

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