10.5152/turkjnephrol.2019.3394

Original Article

Turkish Journal of Nephrology

Prevalence of Vitamin D Deficiency in Patients with Stage 3/4 Chronic Kidney Disease and Its Relation to Secondary Hyperparathyroidism

Ayşe Selcen Pala[1], Eda Kaya[2], Selma Alagöz[1], Sinan Trabulus[1], Murat Bolayırlı[3], Mehmet Rıza Altıparmak[1], Nurhan Seyahi[1]

[1]Department of Internal Medicine, Division of Nephrology, İstanbul University-Cerrahpaşa, Cerrahpaşa School of Medicine, İstanbul, Turkey
[2]İstanbul University-Cerrahpaşa, Cerrahpaşa School of Medicine, İstanbul, Turkey
[3]Department of Biochemistry, İstanbul University-Cerrahpaşa, Cerrahpaşa School of Medicine, İstanbul, Turkey

Abstract

Objective: The extent of bone mineral disorders in predialysis patients is not well defined. This study aimed to detect the prevalence of both 25-hydroxyvitamin D (25(OH)D) and 1,25-dihydroxyvitamin D (1,25(OH)2D) deficiency in patients with stage 3-4 chronic kidney disease (CKD) and its relation to secondary hyperparathyroidism.
Materials and Methods: In this study, 113 patients with stage 3-4 CKD admitted to our outpatient clinic were included. Clinical, demographic, and lifestyle characteristics of patients were recorded. Patients' serum creatinine, calcium, phosphorus, 25(OH)D, 1,25(OH)2D, and parathormone (PTH) levels were measured.
Results: We found that 85 patients (75.2%) had stage 3 CKD, and 28 patients (24.8%) had stage 4 CKD. A low 25(OH)D level was detected in 89.4% of the patients (stage 3 CKD 89.4%, stage 4 CKD 89.3%). The PTH level was higher in patients with low 25(OH)D level with a borderline statistical significance (p=0.057). The number of patients with 1,25(OH)2D level lower than 54.53 pg/ml was 28 (24.77%), which was accepted as a cut-off value. The mean PTH level was significantly higher in the group with lower 1,25(OH)2D (P=0.048). The prevalence of secondary hyperparathyroidism was found as 57.5%.
Conclusion: We found a high prevalence of bone mineral disorders among patients with stage 3–4 CKD. These results point out the importance of timely diagnosis and appropriate treatment.
Keywords: Vitamin D deficiency, secondary hyperparathyroidism, chronic kidney disease, late-stage kidney disease

Corresponding Author: Nurhan Seyahi ✉ nseyahi@yahoo.com
Received: 22.05.2018 **Accepted:** 16.07.2018

Presented in: This study was presented at the "31. National Nephrology, Hypertension, Dialysis and Transplantation Congress", "22-26 October 2014", "Antalya, Turkey".

Cite this article as: Pala AS, Kaya E, Alagöz S, Trabulus S, Bolayırlı M, Altıparmak MR, Seyahi N. Prevalence of Vitamin D Deficiency in Patients with Stage 3/4 Chronic Kidney Disease and Its Relation to Secondary Hyperparathyroidism. Turk J Nephrol 2019; 28(2): 132-7.

INTRODUCTION

Bone mineral disorders are observed from the early stages of chronic kidney disease (CKD). According to the Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guideline on the management of chronic kidney disease-mineral and bone disorders published in 2017, a regular follow-up of serum calcium, phosphorus, parathormone (PTH), alkaline phosphatase, and vitamin D levels is suggested starting from CKD stage 3 (1).

The patients with CKD commonly suffer from 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) deficiency because of lack of 25-hydroxyvitamin D (25(OH)D), which is the precursor form of vitamin D, and decreased activity of 1α-hydroxylase, which converts 25(OH)D into its active form (2). It can be even observed in more than 80% of patients with CKD (3). Low vitamin D levels are associated with increased bone turnover, secondary hyperparathyroidism, and decreased bone mineral density in patients with CKD (4). Moreover, it has been shown that

low vitamin D levels increase risk of progression to dialysis and mortality in patients with predialysis CKD (5).

Despite the high burden of bone mineral disorders, there is lack of systemic studies to reveal the prevalence of vitamin D deficiency and its relation to secondary hyperparathyroidism in predialysis patients.

In this study, we aimed to detect the prevalence of both 25(OH) D and 1,25$(OH)_2$D deficiency in patients with stage 3-4 CKD and its relation to secondary hyperparathyroidism.

MATERIALS AND METHODS

Study Subject and Design

We performed a cross-sectional study in a tertiary-care outpatient clinic center. Between November 2012 and February 2014, we examined medical records of 772 patients. Adult patients (>18 years of age) with an estimated glomerular filtration rate (eGFR) value between 15 and 59 mL/min/1.73 m^2 were eligible for the study. The following exclusion criteria were used: being on a renal replacement treatment; having a malignancy; the presence of primary hyperparathyroidism; severe liver failure; and severe malabsorption. Furthermore, being on treatment with medications containing vitamin D, calcium, and phosphate binding agents, calcimimetic agents, denosumab, and bisphosphonates in the last six months was also considered as an exclusion criterion. According to these criteria, 159 patients were eligible. From these, 113 patients gave an informed consent to be a participant in this study.

eGFR was calculated using Modification of Diet in Renal Disease formula with the latest creatinine value of the patients measured in the last one year.

We used a standardized form to collect information about demographic data, physical activity level, way of dressing, nutritional habits, medications, weight, and height. Adequate sun exposure was defined as exposure of face and arms to sun at least 30 minutes in sunny days according to the patients' declaration (6). Physical activity was classified as sedentary, moderate, and heavy as per the self-assessment of the patients. The patients who did not do moderate exercises, such as running, walking, cycling were recorded as sedentary; the patients who exercised for 30 minutes were recorded as moderate; and those who exercised more than 30 minutes were recorded as heavy. Data on cardiovascular disorders, diabetes, and hypertension were recorded from the patient's files.

To measure serum creatinine, calcium, phosphorus, 25(OH)D, 1,25$(OH)_2$D, and PTH levels, a sample of blood was drawn from the patients.

The study protocol was approved by the local medical ethics committee.

Laboratory Assessment

Serum creatinine, calcium, and phosphorus were analyzed using photometric methods with Abbott Architect c8000 autoanalyzer (Abbott Diagnostics, Abbott Park, IL, USA). The PTH levels were determined by means of the chemiluminescent immunoassay (Liaison N-tact; DiaSorin Inc, Stillwater, MN, USA). Serum calcium levels were corrected according to albumin level. The reference ranges for laboratory parameters were as following: serum creatinine, 0.8-1.3 mg/dL; calcium, 8.9-10.1 mg/dL; and phosphorus, 2.5-4.5 mg/dL.

Measurements and Definition of Laboratory Range for Vitamin D Levels

The 25(OH)D and 1,25$(OH)_2$D levels were measured with ELISA (Eastbiopharm, Hangzhou, China) Catalog no: CK-E10878. A level of 25(OH)D lower than 15 ng/dl was considered as vitamin D deficiency. The threshold for low 1,25$(OH)_2$D was defined by the 25th percentile of patients included in our study, which was the lower percentile (n=28). In accordance with this threshold, low 1,25$(OH)_2$D was determined as 54.53 pg/mL.

Statistical Analysis

Statistical analysis was performed with the SPSS (Statistical Package for Social Sciences for Windows) 17.0 software (SPSS Inc., Chicago, IL, USA). Data were expressed as the median±standard deviation (SD). Normality was determined using histograms, probability graphics, and Kolmogorov-Smirnov/Shapiro-Wilk tests.

The t-test was used for normally distributed variables, and the Mann-Whitney U test was used for non-normally distributed variables. For categorical variables (gender, stage etc.), the chi-square test (Fisher exact test) was used. Correlation was analyzed using Pearson or Spearman correlation tests. $p<0.05$ was considered as statistically significant.

RESULTS

Demographic and Clinical Data

In our study, 113 patients were evaluated. Among the patients, 85 (75.2%) had stage 3 CKD, and 28 (24.8%) had stage 4 CKD. Demographic, clinical data, and lifestyle-related characteristics of the patients stratified by CKD stage are shown in Table 1. The mean age was 59.94±11.6 years. Male sex was more prominent (n=67, 59.3%). The average body mass index (BMI) of the patients was 28.75±5.2 kg/m^2. The most commonly seen comorbid diseases were hypertension (85%), diabetes mellitus (45.1%), and cardiovascular diseases (34.5%).

Only 37.2% of the patients stated an adequate sun exposure, and 33.6% of them had a sedentary lifestyle. Female patients generally preferred to wear hijab (69.6%) that reduces sun exposure. In female patients with stage 3 CKD, 66.7% preferred to wear hijab; and in female patients with stage 4 CKD, 76.4% preferred to wear hijab (p=0.724). Between the two groups,

there was no statistically significant difference regarding those parameters.

Considering nutrition habits, patients consumed on average 4 meals of fish, 13 meals of egg, 14 meals of meat, and 24 meals of milk and milk products in a month. Those amounts might roughly reflect daily intake of 250 IU (7).

Laboratory Findings

We analyzed and presented our laboratory results using two different classifications; first, by grouping the patients according to CKD stage, and second by grouping the patients according to 25(OH)D level.

Patient subgroups classified by CKD stage is shown in Table 2. A low 25(OH)D level was detected in 89.4% of the patients, and this rate did not significantly differ between two stages (stage 3 CKD 89.4%, stage 4 CKD 89.3%). A normal 25(OH)D level was found in 10.6% of the patients, and there was no statistically significant difference between the two groups (stage 3 CKD 10.6%, stage 4 CKD 10.7%, p=1). There was no significant difference between the stages both for $1,25(OH)_2D$ level and 25(OH)D level (Table 2).

In the whole study population, hyperparathyroidism was detected as 57.5%. The frequency of hyperparathyroidism in patients with stage 4 CKD was significantly higher than that of the patients with stage 3 CKD (stage 3 CKD 47.1%, stage 4 CKD

Table 1. Demographic, clinical data, and lifestyle characteristics

	All patients (n=113)	Stage 3 CKD (n=85)	Stage 4 CKD (n=28)	p **
Gender (male %)	59.3	61.2	53.6	0.477
Age (year)	59.94±11.6	60.56±12.2	58.05±9.7	0.321
Body mass index (kg/m^2)	28.75±5.1	28.74±4.8	28.76±5.8	0.161
Diabetes mellitus (%)	45.1	49.4	32.1	0.111
Hypertension (%)	85	88.2	75	0.125
Cardiovascular diseases (%)	34.5	35.3	32.1	0.761
Adequate sun exposure (%)	37.2	38.8	32.1	0.526
25-hydroxyvitamin D 15mcg/L (%)	89.4	89.4	89.3	1
25-hydroxyvitamin D>15 mcg/L (%)	10.6	10.6	10.7	1
Physical activity (%)				
Sedentary	33.6	35.3	28.6	
Adequate	38.9	38.8	39.3	0.746
Active	27.4	25.9	32.1	

CKD: Chronic Kidney Disease
**Comparison of stage 3 and 4 CKD

Table 2. Laboratory results

	CKD (n=113)	Stage 3 CKD (n=85)	Stage 4 CKD(n=28)	p**
Creatinine (mg/dL)	1.51±0.6	1.26±0.3	2.29±0.6	<0.001
Estimated Glomerular Filtration Rate (mL/min 1.73m^2)	40.12±12.1	45.7±7.9	23.14±4.3	<0.001
Calcium (mg/dL)	8.15±0.6	8.14±0.56	8.18±0.62	0.915
Phosphorus (mg/dL)	3.12±0.5	3.09±0.5	3.23±0.48	0.213
PTH (pg/mL)***	89.54±68	68.77±33.5	152.6±102	<0.001
25-hydroxyvitamin D (mcg/L)	10.55±7.6	10.99±8.06	9.21±5.8	0.28
1,25-dihydroxyvitamin D (pg/mL)	83.8±92.7	87.2±95.8	73.5±83.3	0.221

CKD: Chronic Kidney Disease
**Comparison of stage 3 and 4
***(Parathormone) PTH>65 pg/ml: upper limit of the normal range for the laboratory kit

Table 3. Laboratory findings of patients with 25(OH)D level above or below 15 mcg/L

	25(OH)D<15mcg/L (n=101)	25(OH)D>15 mcg/L (n=12)	p*
Gender (male %)	61.4	41.7	0.223
Age (year)	60.1±1.2	58.1±2.7	0.56
Stage 4 (%)	24.8	25	1
BMI (kg/m^2)	28.9±0.5	27.7±1.4	0.45
Diabetes mellitus (%)	44.6	50	0.76
Hypertension (%)	85.1	83.3	1
Cardiovascular disease (%)	38.6	0	0.008
Adequate sun exposure (%)	34.7	58.3	0.125
Patients with sedentary life style (%)	34.7	25	0.748
Creatinine (mg/dL)	1.52±0.6	1.41±0.4	0.63
eGFR (mL/min)	40.04±12	40.75±11.9	0.94
Calcium (mg/dL)	8.18±0.5	7.84±0.9	0.102
Phosphorus (mg/dL)	3.09±0.5	3.4±0.5	0.041
PTH (pg/mL)	91.29±69.2	74.86±64.5	0.057
1,25(OH)2D (pg/mL)	60.33±21.6	281.48±188.8	<0.001

*Comparison of patients with 25(OH)D levels above or below 15 mcg/L

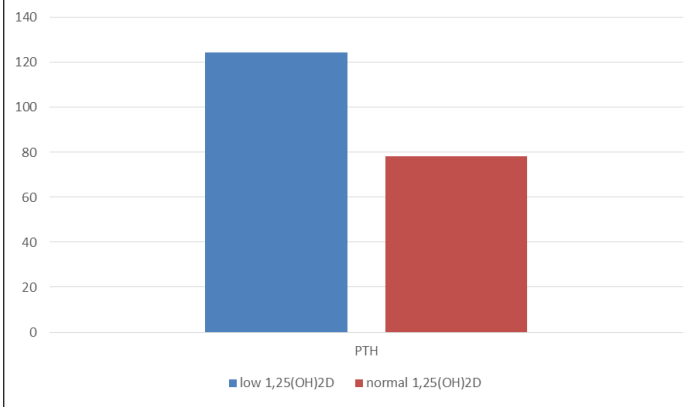

Figure 1. The PTH levels in comparison with low and normal 1,25(OH)2D levels (p=0.048).

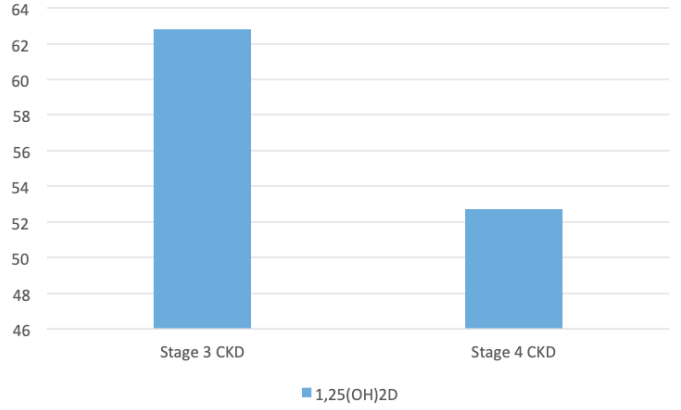

Figure 2. The 1,25(OH)2D levels in patients with stage 3 and 4 CKD with low 25(OH)D (p=0.129).

89.3%, p<0.001). Compared with patients with stage 3 CKD, the PTH levels were also significantly higher in patients with stage 4 CKD (p<0.001) (Table 2).

Hypoparathyroidism (PTH<15 pg/mL; lower limit of the normal range for the laboratory kit) was detected in 0.9% of the patients. There were no significant differences between the two stages (stage 3 CKD 1.2%, stage 4 CKD 0%, p=1).

Hypocalcemia was present in 69% of the patients (stage 3 CKD 69.4%, stage 4 CKD 67.9%), and hypophosphatemia was present in 14.2% of the patients (stage 3 CKD 16.5%, stage 4 CKD 7.1%). There was no patient with hypercalcemia or hyperphosphatemia. The calcium and phosphorus levels were similar between the two stages (p=0.915, p=0.213).

Patient subgroups classified according to 25(OH)D levels are shown in Table 3. The male gender was more common among patients with low 25(OH)D; however, there was no significant difference between the two groups regarding age, CKD stage, BMI, diabetes mellitus, and hypertension. History of cardiovascular disease was more common among patients with low 25(OH)D

levels (p=0.008). In women wearing hijab, a significantly lower level of 25(OH)D was detected (76.9%); on the other hand, 28.6% of women wearing hijab had a 25(OH)D value higher than 15 mcg/L (p<0.02). The creatinine, eGFR, and calcium levels were similar between the two groups. The PTH level was higher in patients with low 25(OH)D level with a borderline statistical significance (p=0.057). The phosphorus and $1,25(OH)_2D$ levels were found significantly lower in patients with low vitamin D level (Table 3).

Finally, we examined the associations among PTH, 25(OH)D and $1,25(OH)_2D$. Compared with patients with a normal $1,25(OH)_2D$ level (78.43±43.15 pg/mL), the PTH level of patients with a low $1,25(OH)_2D$ level was significantly higher (124.38±109.8 pg/mL) (p=0.048) (Figure 1). On the other hand, in patients with low 25(OH)D level (n=101), $1,25(OH)_2D$ levels were not significantly different between patients with stage 3 and stage 4 CKD (62.8±20.4 pg/mL vs. 52.74±23.67 pg/mL; p=0.129) (Figure 2).

DISCUSSION

We detected that 57.3% (n=65) of the patients with stage 3 or stage 4 CKD had hyperparathyroidism. The prevalence of hyperparathyroidism in predialysis patients is between 20% and 60% in various studies (5, 8, 9, 10). Probably this difference in prevalence between different studies is because of a variation of 25(OH)D levels among the study participants. This study revealed a significantly higher frequency of hyperparathyroidism and higher PTH level in patients with stage 4 CKD compared with those in stage 3 CKD. This finding is similar to the previous studies (5, 9, 11).

In 89.4% of the patients, 25(OH)D levels were low. There was no significant difference between stage 3 and 4 CKD considering this finding (p=1). A study with 273 peritoneal dialysis patients from Turkey and Greece showed vitamin D insufficiency in 92% of the patients (12). Another study from Germany found that 74% of 444 patients with an eGFR < 60 mL/min had a 25(OH)D level lower than 20 ng/mL (13). Furthermore, in a study from Canada 34.5% of 168 patients with stage 2-5 CKD (8), in USA 12% of 1814 patients with CKD (5), in another study again in USA 15% of 12763 patients with stage 3-4 CKD (14) had a 25(OH)D level lower than 15 ng/mL. In the UK in a study, 39% of 112 patients with stage 3-4 CKD had vitamin D insufficiency (11). However, in Australia, which is a sunny region, 9.8% of 593 patients with stage 1-5 CKD revealed vitamin D insufficiency (15). In our study, in line with previous data, we also did not detect significantly high phosphorus levels in early stages of CKD (5, 9, 10); on the other hand, hypocalcemia was frequent (69%) in our patients. The high frequency of hypocalcemia is possibly related to low 25(OH)D levels.

Previous studies revealed a decrease in renal functions induces a decreased 1-alpha-hydroxylase activity (5, 8, 9). Although patients with stage 3 CKD revealed a lower $1,25(OH)_2D$ and a higher phosphorus level, there was no significant decrease in $1,25(OH)_2D$ levels in patients with stage 3 CKD compared with those in patients with stage 4 CKD. An increase in PTH levels prevents hyperphosphatemia, and hence because of a disinhibition in 1-alpha-hydroxylase activity, $1,25(OH)_2D$ levels persist as relatively high. This phenomenon can be the cause of statistical insignificance in $1,25(OH)_2D$ decrease.

In patients with low 25(OH)D levels, an expected low $1,25(OH)_2D$ level was detected. Also, a significant lower phosphorus level was found in these patients because of high PTH levels.

According to World Health Organization, daily vitamin D requirement is 400 IU for patients younger than 65 years and 600 IU for patients older than 65 years (16). According to the results of our dietary questionnaire, low vitamin D intake could be considered as an additional causative cause of vitamin D deficiency besides inadequate sun exposure. Considering data of United States Department of Agriculture (USDA) Food Composition Databases, fish, egg, meat, milk, and milk products are basic vitamin D resources. The amount of vitamin D is approximately 40 IU in one egg, 42 IU in 100 g red meat, 120 IU in one cup of milk, and 440 IU in 100 g salmon (7). However, we could not calculate the exact amount of vitamin D intake using our questionnaire, because exact amount of the meals was unknown.

In our study population, the most frequently seen comorbid diseases were hypertension (85%), diabetes mellitus (45.1%), and cardiovascular diseases (34.5%). Other studies support this finding (2, 13). Despite the similar demographic data of the patients with low or normal 25(OH)D levels, we detected a higher frequency of low 25(OH)D level among women who preferred to wear hijab. In the patients with low 25(OH)D level, the frequency of cardiovascular diseases was significantly higher compared with that of the normal 25(OH)D group (p=0.008). This finding is supported by many other studies (5, 8, 13, 14, 17).

Our study has several limitations. Firstly, we were not able to calculate an accurate threshold for low $1,25(OH)_2D$. A study with a larger group can provide a more accurate threshold for $1,25(OH)_2D$. Secondly, we did not compare the patients in this study to a healthy control group. Thirdly, we excluded patients who received any treatment with vitamin D, calcium, phosphate binding agents, calcimimetic agents, denosumab, and bisphosphonates because those medications might interfere with the laboratory parameters that we examined. Additionally, by excluding patients on treatment, we excluded patients with CKD with severe bone mineral metabolism disorders. Our results were possibly affected by this exclusion criterion. Furthermore, we did not collect data on physical activity and nutritional habits using a more detailed and validated questionnaire.

CONCLUSION

A follow-up for bone mineral metabolism disorders is recommended to patients with CKD in predialysis period. An early treatment including the substitution of vitamin D must be considered. For prevention, adequate sun exposure and appropriate nutrition must be advised.

Ethics Committee Approval: Ethics Committee approval was received for this study from the Ethics Committee of İstanbul University-Cerrahpaşa School of Medicine (12.11.2013, 31879).

Informed Consent: Written informed consent was obtained from all patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – N.S., A.S.P. Design – S.A., A.S.P.; Supervision – N.S., A.S.P..; Resource – N.S.,A.S.P.,S.A.; Materials – A.S.P., M.B., S.A.; Data Collection and/or Processing – A.S.P., M.B., S.A..; Analysis and/or Interpretation – A.S.P., E.K., N.S. ; Literature Search – A.S.P., E.K.; Writing – N.S., S.T., E.K., A.S.P.; Critical Reviews – N.S., S.T., M.R.A.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The financial support was provided by Istanbul University Scientific Research Projects Department under grant Project No: 38932.

REFERENCES

1. Kidney-Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease-mineral and bone disorder (CKD-MBD). Kidney Int Suppl 2017; 113: 1-130.
2. Quarles LD. Endocrine functions of bone in mineral metabolism regulation. J Clin Investig 2008; 118: 3820-8. [CrossRef]
3. Ngai M, Lin V, Wong HC, Vathsala A, How P. Vitamin D status and its association with mineral and bone disorder in a multi-ethnic chronic kidney disease population. Clin Nephrol 2014; 82: 231-9. [CrossRef]
4. Mucsi I, Almási C, Deák G, Marton A, Ambrus C, Berta K, et al. Serum 25(OH)-vitamin D levels and bone metabolism in patients on maintenance hemodialysis. Clin Nephrol 2005; 64: 288-94. [CrossRef]
5. Ravani P, Malberti F, Tripepi G, Pecchini P, Cutrupi S, Pizzini P, et al. Vitamin D levels and patient outcome in chronic kidney disease. Kidney Int 2009; 75: 88-95. [CrossRef]
6. Holick MF. McCollum Award Lecture, 1994: vitamin D--new horizons for the 21st century. Am J Clin Nutr 1994; 60: 619-30. [CrossRef]
7. USDA National Nutrient Database for Standard Reference Legacy Release, April 2018.
8. Levin A, Bakris GL, Molitch M, Smulders M, Tian J, Williams LA, et al. Prevalence of abnormal serum vitamin D, PTH, calcium, and phosphorus in patients with chronic kidney disease: results of the study to evaluate early kidney disease. Kidney Int 2007; 71: 31-8. [CrossRef]
9. Hamano T, Fujii N, Matsui I, Nakano C, Inoue K, Tomida K, et al. Guideline-Practice Gap in the Management of Predialysis Chronic Kidney Disease Mineral Bone Disorder in Japan. Ther Apher Dial 2011; 15 Suppl 1: 2-8. [CrossRef]
10. Stavroulopoulos A, Porter CJ, Roe SD, Hosking DJ, Cassidy MJ. Relationship between vitamin D status, parathyroid hormone levels and bone mineral density in patients with chronic kidney disease stages 3 and 4. Nephrology (Carlton) 2008; 13: 63-7.
11. Andress DL, Coyne DW, Kalantar-Zadeh K, Molitch ME, Zangeneh F, Sprague SM. Management of secondary hyperparathyroidism in stages 3 and 4 chronic kidney disease. Endocr Pract 2008; 14: 18-27. [CrossRef]
12. Taskapan H, Ersoy FF, Passadakis PS, Tam P, Memmos DE, Katopodis KP, et al. Severe vitamin D deficiency in chronic renal failure patients on peritoneal dialysis. Clin Nephrol 2006; 66: 247-55. [CrossRef]
13. Pilz S, Tomaschitz A, Friedl C, Amrein K, Drechsler C, Ritz E, et al. Vitamin D status and mortality in chronic kidney disease. Nephrol Dial Transplant 2011; 26: 3603-09. [CrossRef]
14. Navaneethan SD, Schold JD, Arrigain S, Jolly SE, Jain A, Schreiber MJ Jr, et al. Low 25 Hydroxyvitamin D Levels and Mortality in Non-Dialysis-Dependent CKD. Am J Kidney Dis 2011; 58: 536-43. [CrossRef]
15. Petchey WG, Johnson DW, Hawley CM, Isbel NM. Predictors of Vitamin D Status in Predialysis Chronic Kidney Disease Patients: A Cross-sectional Analysis in a High Ultraviolet Climate. J Ren Nutr 2012; 22: 400-8. [CrossRef]
16. World Health Organization (WHO). Vitamin and Mineral Requirements in Human Nutrition, 2nd Edition. Geneva, Switzerland. 2004.
17. Melamed ML, Michos ED, Post W, Astor B. 25-hydroxyvitamin D levels and the risk of mortality in the general population. Arch Intern Med 2008; 168: 1629-37. [CrossRef]