

Effects of Inactive Vitamin D on Persistent Secondary Hyperparathyroidism in Patients on Hemodialysis

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Abstract

Background: Secondary Hyperparathyroidism (sHPT) is an important feature of chronic renal failure and contributes to the development of renal osteodystrophy. This study was carried out to assess 25(OH)D status and its effect on sHPT in patients on hemodialysis (HD).

Methods: A prospective experimental trial of 180 HD patients (F: 81, M: 99, age > 14year) participated in the study. At base line, levels of 25(OH)D, intact Parathyroid Hormone (iPTH), Calcium (Ca), Phosphorous (P), Alkaline phosphatase (Alk p), and albumin of serum were measured. Patients with 25(OH)D deficiency (< 30 ng/mL) were randomly divided to two groups: intervention (received 300,000 U/IM vitD3 at the beginning and after 2 months, if was necessary) and control (received placebo). After 2 and 4 months, the same biochemical markers were measured and efficacy of vitD3 on sHPT was assessed. Secondary Hyperthyroidism (sHPT) was defined as iPTH > 300 pg/mL.

Results: Serum 25(OH)D levels were deficient in 87.8% (n: 158) of subjects, and normal in 12.2% (n: 22). The prevalence of sHPT, according to 25(OH)D levels, was 71.5% (n: 113) (< 30 ng/mL) and 40.9% (n: 9) (\geq 30), respectively. There were 57 intervention and 56 control subjects. In the intervention group, 2 months after injections, 25(OH)D increased from 13.85 ± 6.5 to 48.5 ± 20.7 ($P < 0.001$), iPTH was reduced from 567.2 ± 276.7 to 282.7 ± 183.6 ($P < 0.001$), calcium from 9.10 ± 0.5 to 8.76 ± 0.7 ($P = 0.021$), Alk p from 553.37 ± 495.6 to 393.4 ± 419.5 ($P < 0.001$), albumin from 3.87 ± 0.5 to 4.00 ± 0.4 ($P = 0.06$), and phosphorus from 4.90 ± 1.2 to 5.21 ± 1.3 ($P = 0.12$). Since all cases were under appropriate treatment for sHPT, there was a significant reduction on the levels of iPTH ($P = 0.005$) and Alk p ($P = 0.049$), and slight increase in 25(OH)D level ($P = 0.08$) in the control group. However, the amount of these changes was less than the intervention group.

Conclusions: These findings showed that 25(OH)D insufficiency was highly prevalent in HD cases and higher amount of 25(OH)D levels prevent sHPT.

Keywords: 25-Hydroxy Vitamin D, End Stage Renal Failure, Secondary Hyperparathyroidism, Hemodialysis

1. Introduction

The progression of kidney failure leads to loss of excretory activity and impairment of endocrine functions and mineral metabolism that affects many organ systems. Secondary secretion Parathyroid Hormone (sHPT) is a compensatory mechanism to restore normal levels of serum calcium and phosphorus concentrations, and is associated with high level of PTH (1). The sHPT and high calcium (Ca) \times phosphorus (P) product have been associated with the risk of bone fractures, cardiovascular morbidity and mortality, and parathyroidectomy (2-4).

Common causes of sHPT are associated with deficiency in vitamin D, inadequate calcium foods, and chronic renal failure (5). In patients with uremia, to maintain normal metabolism of the bone, the serum level of PTH should be increased by a factor of two or three of normal cases (6).

Secondary HPT is caused by a complex disorder of min-

eral metabolism involving low vitamin D and elevated PTH levels. The main regulator of 1- α -hydroxylase activity in the kidney is PTH and vitamin D is a regulator of PTH (7). In patients on Hemodialysis (HD), the mainstay of treatment of sHPT is use of activated vitamin D analogues (8), including nonselective agents such as Calcitriol (1, 25(OH)D3) (9).

Current kidney disease outcomes quality initiative (K/DOQI) recommends measuring serum levels of intact parathyroid hormone (iPTH), calcium and phosphorus in stage 3 to 4 chronic kidney disease (CKD) (9). The recommended levels for the iPTH is 150 - 300 pg/mL, and active vitamin D should be administered for the patients. When the level of iPTH is more than 300 pg/mL (9), dosage of vitamin D has to be adjusted.

The NKF-K/DOQI guidelines also recommend that in patients with CKD stage 3 or 4, who have elevated iPTH levels, 25(OH)D3 level should be measured (10) and if levels are less than 30 ng/mL, precursor vitamin D supplement is rec-

ommended (10, 11).

In the general population, low levels of 25(OH)D have been associated with increased PTH levels and studies have shown the precursor of vitamin D controls sHPT (12). However, the role of 25(OH) D in the treatment of renal osteodystrophy in HD patients remains to be determined.

In this study, we aimed at investigating the prevalence of 25(OH) vitamin D deficiencies in HD patients and then evaluate the effect of Vitamin D3 injections in controlling sHPT.

2. Methods

This study was conducted in four HD centers located in Tehran and Zanjan (Vali-e-asr and Beheshti hospitals in Zanjan, and Firozabadi and Haftom-Tir in Tehran) cities of Iran from 2009 to 2010. The study was approved by the ethics committee of metabolic disorder research center of Zanjan, and patients provided their signed consents. The study duration was 4 months.

We determined the prevalence of 25(OH)D deficiency and sHPT in 180 HD participants. The HD patients, who were older than 14 years and had been under HD for at least 6 months were selected for the study. Patients, who had a history of recurrent calcium kidney stones, patients that had received treatment with any medication that interfered with serum levels of vitamin D, patients with vitamin D (oral or injected form) treatment during the preceding 6 months, and patients with a diagnosis of tertiary HPT and advanced liver disease were excluded from the study. Also, patients with a history of parathyroidectomy, uncontrolled hyperphosphatemia, and severe hypercalcemia were excluded.

Patients with level of 25(OH)D less than 30 ng/mL were considered as vitamin D deficient and patients with iPTH above 300pg/mL were known as sHPT (13). Patients were under HD 3 times a week and were treated with calcium carbonate, renagel and calcitriol, according to the level of calcium (Ca), phosphorus (P), and iPTH, which continued during the study.

Fasting blood samples of calcium, phosphorus, alkaline phosphatase, albumin, 25(OH)D, and iPTH were obtained at base line, 2 months, and at the end of the study, if necessary.

Serum pre-dialysis blood samples were tested for calcium by Arsenazo, phosphorus by photometric, alkaline phosphatase by photometric, albumin by Bromocresol Green, 25(OH)D by Acetonitrile, and iPTH level by radioimmunoassay methods.

First, prevalence of 25(OH)D deficiency among patients on HD was evaluated. Then, patients with a lack of 25(OH)D were randomly divided in intervention and

control groups. The interventional group received an intramuscular shot of cholecalciferol (vitamin D3), 300,000 units at the beginning and at the end of 2 months. This re-administration was performed if level of 25(OH)D was still less than 30 ng/mL. The control group received the placebo. Over 2 to 4 months after treatment, the data was collected and compared for the two groups, to assess effects of vitamin D on calcium, phosphorus, $Ca \times P$ and iHPT.

Serum calcium concentration was corrected by serum albumin concentration as follows:

Corrected serum calcium = Serum calcium levels measured + $0.8 \times (4 - \text{albumin serum})$

Duration of dialysis, age, and gender were extracted from the patients' records. Demographic information of patients was collected, as shown in Table 1. The HD protocol for all patients was 4 hours with hemophane membranes, the average blood flow rate was 300 to 350 mL/minute, and bicarbonate basis was used for dialysate.

2.1. Statistical Analysis

Statistical analysis was performed using the SPSS software for windows (version 20). The t test was performed for comparing continuous variables of the 2 groups and paired t test for before and after data. Mann-Whitney U-test and Wilcoxon sign rank tests were used for non-normal variables. All of the statistical tests were 2-sided. P values of less than 0.05 were considered significant.

3. Results

One hundred and eighty participants (81 females (45%) and 99 males (55%)), with a mean age of 56.25 ± 12.67 years were selected for this study. Table 1 presents the characteristics of the participants.

Out of the 180 patients on HD (81 females (45%) and 99 males (55%)), 158 (87.8%) (68 females (43%) and 90 males (57%)), with mean age of 56.15 ± 12.7 were 25(OH)D deficient (< 30 ng/mL) and 22 (12.2%) (13 females (59.1%) and 9 males (40.9%)), with mean age of 56.95 ± 12.2] had 25(OH)D more than 30 ng/mL.

The prevalence of sHPT (PTH > 300), according to vitD levels in patients with vitamin D < 30 ng/mL, was 113 (71.5%) (46 females (40.7%) and 67 males (59.3%)), with mean age of 55.78 ± 12.5 , and the prevalence in patients with vitamin D ≥ 30 ng/mL was 9 (40.9%) (4 females (44%) and 5 males (56%)), with mean age of 61.56 ± 8.3 .

Patients with vitamin D deficiency, who had sHPT, were randomly divided to intervention and control groups. There was not statistically significant difference between

Table 1. Baseline Characteristics of the Study Population^a

| | Total | 25(OH)D < 30 ng/mL | 25(OH)D ≥ 30 ng/mL | P Value |
|----------------------------|----------------|--------------------|--------------------|----------------------|
| Age, y | 56.25 ± 12.6 | 56.15 ± 12.7 | 56.95 ± 12.2 | 0.78 ^b |
| Gender | N = 180 | N = 158 | N = 22 | 0.15 |
| | F: 81 (45) | F: 68 (43) | F: 13 (59.1) | |
| | M: 99 (55) | M: 90 (57) | M: 9 (40.9) | |
| BMI, kg/m ² | 24.90 ± 3.4 | 24.94 ± 3.4 | 24.61 ± 3.1 | 0.66 |
| Duration of dialysis, y | 3.21 ± 1.8 | 3.32 ± 1.8 | 2.41 ± 1.4 | 0.024 |
| Alb, mg/dL | 3.83 ± 0.6 | 3.84 ± 0.6 | 3.76 ± 0.5 | 0.48 ^b |
| Ca, mg/dL | 9.24 ± 0.8 | 9.22 ± 0.8 | 9.42 ± 0.9 | 0.32 |
| P, mg/dL | 4.97 ± 1.5 | 4.93 ± 1.5 | 5.25 ± 1.4 | 0.11 ^b |
| Ca × P | 45.84 ± 13.7 | 45.32 ± 13.6 | 49.58 ± 13.9 | 0.17 ^b |
| Bun | 59.73 ± 17.0 | 60.9 ± 17.6 | 57.18 ± 11.5 | 0.57 |
| Cr | 8.36 ± 2.5 | 8.19 ± 2.3 | 7.40 ± 1.8 | 0.08 |
| Alkaline phosphatase, IU/L | 501.24 ± 419.3 | 507.39 ± 408.4 | 503.05 ± 512.3 | 0.23 ^b |
| 25(OH)D, ng/mL | 17.29 ± 14.7 | 13.48 ± 6.4 | 49.41 ± 17.9 | < 0.001 ^b |
| iPTH, pg/mL | 486.87 ± 327.9 | 460.03 ± 263.8 | 329.7 ± 312.1 | 0.011 ^b |
| iPTH | | | | < 0.001 |
| < 150 | 24 (13.3) | 14 (8.9) | 10 (45.5) | |
| 150 - 300 | 34 (18.9) | 31 (19.6) | 3 (13.6) | |
| ≥ 300 | 122 (67.8) | 113 (71.5) | 9 (40.9) | |

Abbreviations: Alb, Albumin; Ca, calcium; P, Phosphorus; 25(OH)D, 25-hydroxy vitamin D; iPTH, intact parathyroid hormone.

^aValues are expressed as mean ± standard deviation or No. (%).

^bMann-Whitney U test.

the two groups at the baseline in terms of gender, age, duration of HD, blood urea nitrogen (BUN), Alb, Ca, Creatinine (Cr), P, and serum levels of 25(OH)D and iPTH ($P > 0.05$), as shown in [Table 2](#).

The mean of body mass index (BMI) was 24.91 ± 3.3 kg/m² in the intervention group and 24.88 ± 2.8 kg/m² in the control group ($P = 0.78$). There was no statistically significant correlation between serum 25(OH)D levels, serum albumin ($P = 0.43$), and BMI ($P = 0.59$).

Two months after the first intramuscular shot of vitamin D₃, blood levels of Ca, P, Alk p, iPTH, and 25(OH)D serum were compared between the 2 groups as shown in [Table 3](#).

In the intervention group, consisting of 57 patients, 2 months after the first injection, 51 (89.5%) patients obtained a 25(OH)D level, which was increased from 13.85 ± 6.5 to 48.5 ± 20.7 ($P < 0.001$), and 6 (10.5%) patients had 25(OH)D level, which was less than 30 ($P < 0.001$).

In the control group consisting of 56 patients, 5 (8.9%) patients had 25(OH)D level, which was increased and 51 (91.9%) patients had 25(OH)D level, which was less than 30.

In total, 25(OH)D level increased from 11.93 ± 5.3 to 13.75 ± 8.8 , ($P = 0.08$). Thus, the intervention group showed significant changes in comparison to the control group.

In the intervention group with 57 patients, 2 months after the first injections, in 44 (77.2%) patients, amounts of iPTH was reduced from 567.2 ± 276.5 to 282.7 ± 183.6 , ($P < 0.001$). However, in the control group, there was no significant change in the amount of iPTH. Changes in other factors in both groups before and after the intervention are shown in [Table 3](#).

Two months after the first intramuscular shot of vitamin D₃, 6 patients in the intervention group still had 25(OH)D level of less than 30 ng/mL and received 300,000 units of vitamin D₃, as the beginning of the study.

Two months after the treatment, the data was collected and efficacy of vitamin D₃ on calcium, phosphorus, Ca × P, and iPTH was assessed and analyzed. In 6 patients, 25(OH)D level had reached the normal range and in 5 patients, iPTH level was reached less than 300 pg/mL.

The results of analysis of various parameters were as follows; 25(OH) D, 45.63 ± 24.7 ; iPTH, 201.16 ± 90.5 ; cal-

Table 2. Baseline Laboratory Features of Intervention and Control Groups

| Variables | Intervention | Control | P Value |
|----------------------------|----------------|----------------|-------------------|
| Gender, F/M | F: 26 (45.6) | F: 20 (35.7) | 0.35 |
| | M: 31 (54.4) | M: 36 (64.3) | |
| Age, y | 55.28 ± 12.9 | 56.29 ± 12.2 | 0.67 |
| Duration of dialysis, y | 3.72 ± 2.5 | 3.09 ± 1.2 | 0.44 |
| BMI, kg/m ² | 24.91 ± 3.3 | 24.88 ± 2.8 | 0.78 |
| Alb, mg/dL | 3.87 ± 0.5 | 3.85 ± 0.4 | 0.81 |
| Ca, mg/dL | 9.10 ± 0.5 | 9.05 ± 0.9 | 0.75 |
| Alkaline phosphatase, IU/L | 553.37 ± 495.6 | 556.30 ± 436.6 | 0.33 ^a |
| P, mg/dL | 4.91 ± 1.2 | 5.29 ± 1.7 | 0.45 ^a |
| Ca × P | 44.47 ± 10.1 | 47.92 ± 16.7 | 0.46 ^a |
| Cr | 8.81 ± 1.8 | 8.29 ± 2.2 | 0.16 |
| Bun | 64.5 ± 17.4 | 60.59 ± 18.3 | 0.25 |
| iPTH, pg/mL | 567.23 ± 276.7 | 575.21 ± 162.4 | 0.09 ^a |
| 25(OH)D, ng/mL | 13.86 ± 6.5 | 11.93 ± 5.3 | 0.16 ^a |

^aMann Whitney U test.

cium, 9.05 ± 0.8 ; P, 4.9 ± 1.4 ; albumin, 3.78 ± 0.39 ; and ALK p, 291.50 ± 127.35 . A few remaining number of interventional group were not compared with control group.

From 57 patients of the intervention group, for whom iPTH levels were more than 300 pg/mL at the beginning of the study, 2 months after first injection of vitamin D3, iPTH in 10 (17.5%) patients was reduced to less than 150 (pg/mL) and in 34 (59.6%) patients, iPTH was within the range of 150 to 300 (pg/mL). While the amount of iPTH in all patients in the control group remained above 300 pg/mL, no significant reduction was observed.

4. Discussion

One billion people in the world have lack or insufficient levels of vitamin D (14). Vitamin D deficiency and insufficiency is common in patients with chronic kidney disease. Patients with kidney failure are at greater risk of this deficiency (15). Higher levels of 25(OH) D are associated with better survival in patients with renal failure (16).

Cholecalciferol (vitamin D3) is a simple, well tolerated, and inexpensive supplement. We administrated 300,000 IU of intramuscular vitamin D3 at baseline and 2 months later to keep the serum 25 (OH) D levels within the desired range. Our patients were under treatment of calcium phosphate binder (carbonate calcium and sevelamer) along

with calcitriol. The effect of vitamin D3 on some variables such as serum calcium, phosphor, alkaline phosphates, product $Ca \times P$, and iPTH was evaluated.

This study showed that the majority of patients on HD (87.8%) had insufficient levels of 25(OH)D. However, other studies reported the prevalence of 25(OH)D deficiency as 80%, 97%, and 95.5% in patients on dialysis (15-17).

A number of studies have reported a prevalence for 25(OH)D deficiency that is lower than our results. Elisa Del Valle reported a prevalence of only 22.6% among patients on HD (18) and Guillermo suggested that 50% of patients with end-stage renal disease (ESRD) had low level of 25(OH)D (19).

The difference between results of various studies is probably related to race, nutrition status, environment situation, and/or amount of sun exposure.

In a study published in 2008, among 64 HD patients, serum 25(OH) D level had increased by 95% with 20,000 IU of VitD3 per week for 9 months and at the end of the study, serum 25(OH) D had reached more than 30 ng/mL in 48% of patients (20). In another study performed on 107 HD patients with vitamin D deficiency, 100,000 IU of vitamin D3 was administered per month. After 15 months, over 90% of patients had serum 25(OH) D levels of more than 43 ng/mL (21).

In this study, patients were administered 300,000 IU of vitamin D3 at baseline and 2 months later, according to the severity of 25(OH) D deficiency. Serum 25(OH) D levels after the first injection during 2 months, increased to more than 30 ng/mL in 89.5% (51 out of 57) of patients. Patients in this study, reached the desired level of 25(OH)D in a shorter time, which may be related to the amount of vitamin D3 used or the race of the patients.

Multiple studies have examined the effect of vitamin D on serum PTH level in dialysis patients (22, 23). In dialysis patients, 25(OH) D, independent of 1, 25(OH)D3, could increase the absorption of calcium and phosphorus from the intestine and kidney (22). Also, 25(OH) D has a correlation with serum PTH level and indirect effect on bone absorption (23).

In this study, 67.8% of patients had hyperparathyroidism and there was a significant relationship between lack of 25(OH) D and hyperparathyroidism ($P < 0.001$). Our study showed that vitamin D3 combined with calcitriol increases 25(OH) D ($P < 0.001$), significantly reduces iPTH ($P < 0.001$) and Ca ($P = 0.005$), and significantly increases the serum albumin level ($P = 0.06$).

Geoffrey et al. examined the effect of combination therapy of cinacalcet with a low dose of vitamin D to control the concentration of calcium, phosphorus, and iPTH, patients on dialysis, who had sHPT (24). Patients had been administered 180 to 30 mg of vitamin D, once daily for 8 weeks,

Table 3. Comparison of Different Variables Between the Groups Two Months After Vitamin D3 Therapy

| Variables | Intervention (n = 57) | | | Control (n = 56) | | | Difference in Intervention Group | Difference in Control Group | P Value ^a |
|-------------|-----------------------|----------------|----------------------|------------------|----------------|----------------------|----------------------------------|-----------------------------|----------------------|
| | Baseline | After 2 months | P Value ^b | Baseline | After 2 Months | P Value ^b | | | |
| 25(OH) D | 13.85 ± 6.5 | 48.5 ± 20.7 | < 0.001 | 11.93 ± 5.3 | 13.75 ± 8.8 | 0.08 | 34.6 ± 22.4 | 1.82 ± 6.0 | < 0.001 |
| iPTH, pg/mL | 567.2 ± 276.7 | 282.7 ± 183.6 | < 0.001 | 575.2 ± 162.4 | 553.3 ± 179.0 | 0.005 | -284.4 ± 168.3 | -21.89 ± 130.7 | < 0.001 |
| Alb, mg/dL | 3.87 ± 0.5 | 4.00 ± 0.4 | 0.068 | 3.85 ± 0.4 | 4.05 ± 0.5 | 0.021 | -0.15 ± 0.6 | -0.19 ± 0.6 | 0.94 |
| Ca, mg/dL | 9.10 ± 0.5 | 8.76 ± 0.7 | 0.005 | 9.05 ± 0.9 | 8.96 ± 0.8 | 0.31 | 0.34 ± 0.8 | 0.09 ± 0.6 | 0.067 |
| P, mg/dL | 4.90 ± 1.2 | 5.21 ± 1.3 | 0.100 | 5.29 ± 1.7 | 5.08 ± 1.4 | 0.12 | -0.30 ± 1.5 | 0.20 ± 0.6 | 0.021 |
| Ca × P | 44.43 ± 10.8 | 45.21 ± 10.6 | 0.44 | 47.92 ± 16.7 | 45.77 ± 14.6 | 0.13 | 0.74 ± 14.1 | -2.14 ± 9.5 | 0.12 |
| Alk p, IU/L | 553.37 ± 495.6 | 393.4 ± 419.5 | < 0.001 | 556.3 ± 496.7 | 496.7 ± 363.9 | 0.049 | 159.9 ± 237.1 | 59.6 ± 184.9 | 0.011 |

^aMann Whitney U test.^bWilcoxon sign ranks test.

and 2 months later the effect of treatment was checked. They concluded that low levels of vitamin D combined with cinacalcet effectively reduces iPTH and product Ca × P.

Other studies have shown that administration of vitamin D2 improves deficient and insufficient level of 25(OH)D in patients on HD (25) and reduces the level of iPTH. These studies have also claimed that the precursor of vitamin D is not toxic and is effective for the prevention of renal osteodystrophy (26, 27).

Klantrzadh evaluated the results of 9 studies and found that supplementation of vitamin D, whether in oral or injection form, increases 25(OH)D level and declines iPTH level (19). The result of our study showed the same findings.

However, there is another study that showed a lack of inactive vitamin D is not associated with sHPT (28), and Vit D2 or Vit D3 are not able to suppress iPTH (29-32).

4.1. Summary

The role of 25(OH)D in the treatment of sHPT in patients on HD is unclear. In the present study, we assessed the prevalence of 25(OH)D deficiency among patients on HD and evaluated the effect of vitamin D3 in the control of sHPT.

The results of this study indicate that 25(OH)D deficiency was highly prevalent (87.8%) in patients on HD, and it seemed that lower values are not related to gender. A correlation between serum level of vitamin D and BMI was not significant ($r = -0.04$).

Vitamin D3 had an effect on suppression of sHPT ($P < 0.001$). To the best of our knowledge, currently, there is no Iranian epidemiologic study for evaluation of prevalence of 25(OH)D deficiency in HD patients and its effects on iPTH. The results of this work showed that combined therapy of calcitriol and vitamin D3, effectively reduces plasma levels of iPTH and Ca among patients with sHPT. Since this strategy is a relatively new approach in clinical trials, further work is required to identify whether correction of 25(OH) D levels improves control of sHPT.

4.2. Limitation

In terms of follow up, there was no limitation since patients came to HD centers to perform HD. However, we need more patients during longer time periods to confirm our results.

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Footnote

Conflict of interest: None.

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