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25 (OH) VITAMIN D DEFICIENCY IN HEMODIALYSIS (HD) PATIENTS AND A MATCHING SAMPLE OF THE GENERAL POPULATION: EXPERIENCE OF ONE CENTER
A Pilot Study

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ABSTRACT • Introduction : 25 (OH) vitamin D plays an important role in many places through the body. Its deficiency can cause rickets or osteomalacia. This is particularly important in hemodialysis (HD) patients who are at icreased risk due to decreased sunlight exposure and deterioration of their mineral homeostasis. **Objectives** : To determine the prevalence of 25 (OH) vitamin D deficiency in HD patients at Rafic Hariri University Hospital (RHUH), compared to a sample of the general population matched for gender and age, and to evaluate the effectiveness of 25 (OH) vitamin D supplementation in HD deficient group. **Methods** : This is a cross sectional study conducted since December 2012, comparing the prevalence of 25 (OH) vitamin D deficiency in HD patients in the dialysis center at RHUH, with patients from the general population who sought medical attention at RHUH for purposes other than HD, matched for age and gender. 25 (OH) vitamin D levels were measured with radioimmunoassay method (LOINC) at CIC European Lab, Barcelona, Spain. A pilot study was conducted with the 34 HD patients who turned out to be deficient or insufficient in 25 (OH) vitamin D. We supplemented them with cholecalciferol over 6 months. We then assessed their vitamin D levels, and biochemistry parameters. **Results** : The prevalence of 25 (OH) vitamin D deficiency in the sample of HD patients at baseline was 32% while that of insufficiency was 36%. The prevalence of 25 (OH) vitamin D deficiency in the sample of general population was 67%. No correlation was found between 25 (OH) vitamin D levels and the studied parameters. In the pilot study, after six months of cholecalciferol supplementation, there was a significant improvement in 25 (OH) vitamin D levels in the deficient and insufficient groups. **Conclusion**: The sample studied in the general population showed high prevalence of 25 (OH) vitamin D deficiency (67%). The sample studied in HD patients showed a prevalence of 25 (OH) vitamin D deficiency of 32% and insufficiency of 36%. The pilot study showed that 25 (OH) vitamin D supplementation in the form of cholecalciferol is beneficial in HD patients.

Keywords : 25 (OH) vitamin D, hemodialysis, parathyroid hormone, calcium

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Kabalan SN, Jabbour M, Mansour A, Abi Fadel S, Albeaini M. Carence en 25 (OH) vitamine D chez les patients hémodialysés et un échantillon apparié de la population générale : l'expérience d'un centre. Une étude pilote. J Med Liban 2016 ; 64 (2) : 72-77.

RÉSUMÉ • Introduction : La 25 (OH) vitamine D [25(OH)D] joue un rôle important à travers tout le corps. Sa carence peut provoquer le rachitisme ou l'ostéomalacie. Les patients hémodialysés sont particulièrement à risque vu la diminution de l'exposition au soleil ainsi que la détérioration de leur homéostasie minérale. **Objectifs** : Déterminer la prévalence de la carence en 25(OH)D chez les patients hémodialysés au centre de dialyse du centre hospitalier universitaire Rafic Hariri (RHUH) par rapport à un échantillon de la population générale, apparié pour l'âge et le sexe, ayant visité RHUH pour des raisons autres que celles des pathologies rénales, et évaluer les effets de la supplémentation en 25(OH)D chez les patients hémodialysés souffrant d'une déficience. **Méthodes** : Cette étude transversale a été conduite à partir de décembre 2012, comparant la prévalence de la carence en 25(OH)D chez les patients hémodialysés à RHUH avec les patients de la population générale. La 25(OH)D a été mesurée par la méthode de dosage radioimmunologique au laboratoire européen CIC, Barcelone, Espagne. Une étude pilote a été réalisée avec les 34 patients hémodialysés souffrant d'une carence ou d'une insuffisance en 25(OH)D à qui nous avons prescrit du cholécalciférol pour 6 mois. Nous avons ensuite évalué les valeurs de la 25(OH)D et certains paramètres biochimiques. **Résultats** : Le pourcentage de carence en 25(OH)D dans l'échantillon des patients hémodialysés évalués était de 32%, celui de l'insuffisance était de 36%. Concernant la population générale, ce pourcentage était de 67%. Aucune corrélation n'a été trouvée entre les niveaux de 25(OH)D et les paramètres étudiés. Dans l'étude pilote, après 6 mois de supplémentation en cholécalciférol, une amélioration significative du taux de 25(OH)D a été constatée chez les patients souffrant de carence ou d'une insuffisance. **Conclusion** : L'échantillon de population générale étudié avait une forte prévalence de carence en 25(OH)D (67%). Chez les patients hémodialysés, le pourcentage de carence en 25(OH)D était de 32% et celui de l'insuffisance de 36%. L'étude confirme l'efficacité de la supplémentation en 25(OH)D sous forme de cholécalciférol chez les patients hémodialysés.

INTRODUCTION

25 (OH) vitamin D deficiency is highly prevalent in most of the world, and affects a wide spectrum of the public. The prevalence of 25 (OH) vitamin D deficiency in the general population depends upon the definition used (less than 20 or less than 30 ng/ml). In the National Health and Nutrition Examination Survey (NHANES)

2000-2004, more than 30% of participants aged 12 years and older had 25 (OH) vitamin D levels below 20 ng/ml (50 nmol/L) [1]. Over 70% of the same age group had levels below 32 ng/ml (the proportion less than 30 ng/ml was not specified). Thus by either definition suboptimal 25 (OH) vitamin D levels are common [2].

Years ago, nephrologists recommended using vitamin D in hemodialysis (HD) patients, but they mainly used active vitamin D. In 2009, the Kidney Disease Improving Global Outcomes (KDIGO) suggested that vitamin D deficiency and insufficiency be corrected using treatment strategies recommended for the general population in patients with chronic kidney disease (CKD) stages 3-5D [3].

The internationally accepted definition of vitamin D deficiency is a blood concentration less than 20 ng/ml according to KDIGO 2012 where it was suggested not to routinely prescribe vitamin D supplements or vitamin D analogs, in the absence of suspected or documented deficiency, to suppress elevated parathyroid hormone (PTH) concentrations in people with CKD not on dialysis [4].

25 (OH) vitamin D deficiency may result in rickets or osteomalacia and in the general population it has been associated with an increased risk of fractures [5], cancer [6], cardiovascular [7] and autoimmune diseases [8]. A meta analysis of 10 prospective observational studies found an association between low serum 25 (OH) vitamin D levels and early mortality in patients on HD, although no definite proof of causality was obtained [9].

25 (OH) vitamin D deficiency is highly prevalent among patients with CKD [10] who are at high risk due to the fact that they are mostly elderly, have poor intestinal absorption and lack sun exposure. In addition, as kidney function declines, there is a progressive deterioration in mineral homeostasis, with a disruption of normal serum and tissue concentrations of phosphorus and calcium, and changes in circulating levels of hormones. These include PTH, 25-hydroxy-vitamin D [25(OH)D], 1,25-dihydroxyvitamin D [1,25 (OH)2D], and other vitamin D metabolites, fibroblast growth factor-23 [FGF-23], and growth hormone. [3]

The plasma 1,25 $(OH)_2$ vitamin D concentration is a function both of the availability of 25 (OH) vitamin D and of the activities of the renal enzymes 1 alpha hydroxylase and 24 alpha hydroxylase.

Only limited data is available on 25 (OH) vitamin D deficiency in HD patients.

This study aims at determining the prevalence of 25 (OH) vitamin D deficiency in HD patients at Rafic Hariri Univerity Hospital (RHUH) compared to a sample of the general population, matched for age, gender and geographic location and to assess the relation between 25 (OH) vitamin D levels and other parameters of mineral metabolism.

The study aims also at evaluating the effectiveness and safety of 25 (OH) vitamin D supplementation in the HD deficient and insufficient groups.

SUBJECTS AND METHODS

Study design

This is a cross-sectional study conducted since December 2012, comparing the prevalence of 25 (OH) vitamin D deficiency in HD patients in the dialysis center at RHUH, with patients from the general population who sought medical attention at RHUH for purposes other than HD, matched for age and gender. Excluded were patients younger than 18 years old, those previously diagnosed with osteoporosis, patients known to have CKD and patients hospitalized for acute conditions. Fifty HD patients were randomly selected and were kept on their usual medications; 300 patients of the general population were randomly selected from a data of 500 patients.

25 (OH) vitamin D levels as well as PTH, calcium, phosphorus, albumin, alkaline phosphatase and SGPT were measured in HD patients at baseline and six months later. 25 (OH) vitamin D deficiency was defined as a serum 25 (OH) vitamin D level of less than 20 ng/ml for the general population [1]. In CKD patients 25 (OH) vitamin D level deficiency was defined as less than 20 ng/ml and insufficiency between 20 and 30 ng/ml [4,11].

A pilot study was then conducted with the 34 HD patients who turned out to be deficient or insufficient in 25 (OH) vitamin D, where we supplemented them with 25 (OH) vitamin D (cholecalciferol) over six months; we then assessed their 25 (OH) vitamin D levels and other biochemistry parameters.

Supplementation regimen was as follows:

- Individuals who turned out to be deficient in 25 (OH) vitamin D were supplemented with 50 000 IU of cholecalciferol only once/week for six weeks, followed by 10000 IU/week for the remaining time.
- Individuals who turned out to be insufficient in 25 (OH) vitamin D were supplemented with 10000 IU of cholecalciferol weekly for six months [12].

All patients gave written consent. Compliance of these patients was assessed monthly through direct contact with the patients during dialysis sessions. Four patients were lost to follow-up.

Analytical methods

25 (OH) vitamin D levels were measured by radioimmunoassay method (LOINC) at CIC European Lab, Barcelona, Spain, as it is usually the case for serum vitamin D tests in RHUH laboratories. All of the remaining parameters were measured at RHUH laboratories, Beirut.

PTH was measured by electrochemiluminescence immunoassay (ECLIA) on Elecsys 2010, Roche Diagnostics, Mannheim, Germany.

Measurement of calcium was done by o-cresolphthalein complexone method, phosphorus by phoshomolybdate reduction, alkaline phosphatase by 4-nitrophenyl phosphate method, and albumin by bromocresol green dye binding. These assays were done on Cobas Integra 400 Plus, Roche Diagnostics, Mannheim, Germany.

Statistical methods

Concerning univariate descriptive analysis, we used frequencies and percentages for categorical variables and we used means and standard deviation for numeric continuous variables.

For bivariate differential analysis, we used percentage differences and χ^2 tests for categorical variable and tests of means comparison for continuous variables.

For means comparison, independent samples t-test was used when measurements were compared at the same point in time across two different attributes of the independent variable while paired t-test was used when we compared the same subjects across two time periods before and after a therapeutic intervention.

In all t-tests used, 0.05 was adopted as a cutoff value of statistical significance.

RESULTS

Prevalence of 25 (OH) vitamin D deficiency

The prevalence of 25 (OH) vitamin D deficiency in the sample of general population was 67%.

The sample studied in HD patients showed a prevalence of 25 (OH) vitamin D deficiency of 32% and insufficiency of 36%.

Correlation between 25 (OH) vitamin D levels and other parameters

In the general population, the correlation between 25 (OH) vitamin D levels in ng/ml and age was very weak and not significant (Pearson r = 0.227). The same result applied to HD patients (Pearson r = 0.42; *p* value = 0.771) which means that 25 (OH) vitamin D levels were not affected by our patients' age.

In addition, the correlation between 25 (OH) vitamin D levels (ng/ml) and gender in HD patients was not significant (*p* value = 0.663) meaning that there was no significant difference in 25 (OH) vitamin D levels between males and females.

Moreover, there was NO correlation between 25 (OH) vitamin D and PTH, corrected calcium, phosphorus, alkaline phosphates and albumin (Pearson r and *p* values are provided in Table I).

TABLE I

CORRELATION BETWEEN VITAMIN D LEVELS (ng/ml) & PTH, CORRECTED Ca, P, ALK phos, ALBUMIN IN HD PATIENTS

	Pearson Correlation (r)	*p* Value
PTH (pg/ml) at 0 month	–.055	.708
Corrected calcium (mg/dl) at 0 month	–.138	.356
Phosphorus (mg/dl) at 0 month	.040	.785
Alkaline phosphatase (U/L) at 0 month	.095	.517
Albumin (g/dl) at 0 month	.184	.216

PTH: parathyroid hormone **HD:** hemodialysis

Correlation between 25 (OH) vitamin D levels and other parameters after six months of cholecalciferol supplementation

In the treated group, there was a significant improvement in 25 (OH) vitamin D levels (*p* value = 0.009) after 6 months of cholecalciferol supplementation (Table II).

TABLE II

DIFFERENCE IN VITAMIN D LEVELS (ng/ml) BETWEEN 0 AND 6 MONTHS IN THE TREATED GROUP

		Mean	N	Standard Deviation
Pair 1	At 0 month: vitamin D level	19.397	30	7.4134
	At 6 months: vitamin D level	27.897	30	15.7368

However, there was a reduction in the mean of corrected calcium levels between 0 and 6 months of treatment but this was not statistically significant (*p* value = 0.267) (Table III).

TABLE III

DIFFERENCE IN CORRECTED CALCIUM LEVELS (mg/dl) BETWEEN 0 AND 6 MONTHS IN THE TREATED GROUP

		Mean	N	Standard Deviation
Pair 1	At 0 month: corrected calcium	8.67869	26	.947648
	At 6 months: corrected calcium	8.45462	26	.870292

In addition, there was NO statistical significant difference between phosphorus means at 0 and 6 months of treatment (*p* value = 0.105) (Table IV).

TABLE IV

DIFFERENCE IN PHOSPHORUS LEVELS (mg/dl) BETWEEN 0 AND 6 MONTHS IN THE TREATED GROUP

		Mean	N	Standard Deviation
Pair 1	At 0 month: phosphorus	4.7073	30	1.52545
	At 6 months: phosphorus	5.2633	30	1.95333

Concerning PTH, there was NO statistically significant difference between PTH means at 0 and 6 months of treatment (*p* value = 0.987) (Table V).

TABLE V

DIFFERENCE IN PARATHYROID HORMONE (PTH) LEVELS (pg/ml) BETWEEN 0 AND 6 MONTHS IN THE TREATED GROUP

		Mean	N	Standard Deviation
Pair 1	At 0 month: PTH	397.927	26	318.8963
	At 6 months: PTH	397.0135	26	299.16884

Finally, there was NO statistically significant difference between albumin (Table VI) and alkaline phosphatase (Table VII) means at 0 and 6 months of treatment (*p* values = 0.654 and 0.443 respectively).

TABLE VI

DIFFERENCE IN ALBUMIN LEVELS (g/dl) BETWEEN 0 AND 6 MONTHS IN THE TREATED GROUP

		Mean	N	Standard Deviation
Pair 1	At 0 month: albumin	4.1165	26	.88691
	At 6 months: albumin	4.1962	26	.47818

TABLE VII

DIFFERENCE IN ALKALINE PHOSPHATASE (U/L) BETWEEN 0 AND 6 MONTHS IN THE TREATED GROUP

		Mean	N	Standard Deviation
Pair 1	At 0 month: alkaline phosphatase	103.543	30	44.8193
	At 6 months: alkaline phosphatase	118.3533	30	94.14120

Comparison between treated and non treated group statistics Refer to Tables VIII and IX.

TABLE VIII

COMPARISON BETWEEN TREATED AND NON TREATED GROUPS • GROUP STATISTICS

		Number of Subjects Group Status		Mean Group Status		Standard Deviation Group Status	
		Non Treated	Treated	Non Treated	Treated	Non Treated	Treated
Albumin	At 0 month	15	32	4.3	4.2	.8	.5
	At 6 months	14	28	3.8	4.2	.4	.8
Phosphorus	At 0 month	15	34	5.0	4.8	1.6	2.0
	At 6 months	15	30	4.5	5.3	1.6	1.5
Corrected Calcium	At 0 month	15	32	8.5	8.7	.7	.9
	At 6 months	14	28	9.1	8.4	.9	.9
Vitamin D level	At 0 month	16	34	40.2	19.3	8.0	7.0
	At 6 months	15	30	35.1	27.9	22.3	15.7
Alkaline phosphatase	At 0 month	15	34	123.9	100.8	62.1	45.4
	At 6 months	15	30	124.0	118.4	69.6	94.1
Parathyroid hormone	At 0 month	15	32	351.1	397.9	392.1	337.9
	At 6 months	15	28	415.1	397.0	411.2	297.5

TABLE IX

COMPARISON BETWEEN TREATED AND NON TREATED GROUPS P-VALUES FOR GROUP STATISTICS

		T-T test for Equality of Means		
		Sig. (2-tailed)	95% CI of the difference Lower	Upper
Vitamin D level	At 0 month	.000	16.4	25.4
	At 6 months	.218	-4.4	18.7
Corrected Calcium	At 0 month	.460	-.7	.3
	At 6 months	.018	.1	1.3
Phosphorus	At 0 month	.778	-.8	1.1
	At 6 months	.207	-1.9	.4
Parathyroid hormone	At 0 month	.770	-256.8	191.5
	At 6 months	.932	-210.8	229.4
Albumin	At 0 month	.563	-.3	.6
	At 6 months	.029	-.8	.0
Alkaline phosphatase	At 0 month	.152	-8.8	54.8
	At 6 months	.838	-49.8	61.1

CI: confidence interval

N.B. The following table represents the different age groups of hemodialysis (HD) patients at the beginning of the study with their` corresponding means of vitamin D levels.

Hemodialysis (HD) patients						
Age group	18-29	30-39	40-49	50-59	60-69	> 69
Number	4	6	13	12	13	2
Vitamin D mean (ng/ml)	24.50	25.15	27.00	24.12	28.35	16.004

DISCUSSION

This study aimed at determining the prevalence of 25 (OH) vitamin D deficiency in a HD patient group selected randomly from the dialysis center in RHUH, compared to a sample of the general population seeking medical attention, selected randomly from the same hospital.

In the pilot study, the aim was to determine the effect of cholecalciferol supplementation in the 25 (OH) vitamin D deficient and insufficient groups and its effect on other chemistry parameters such as PTH, corrected calcium and others.

At the initiation of the study, the sample studied in the general population showed high prevalence of 25 (OH) vitamin D deficiency (67%). The sample studied in HD patients showed a prevalence of 25 (OH) vitamin D deficiency of 32% and insufficiency of 36%.

The HD patients result was expected and can be attributed to the lack of sun exposure in addition to their kidney failure and the insufficient dietary sources in order to satisfy daily requirements of vitamin D. Concerning the general population, the deficiency of 25 (OH) vitamin D returned to inadequate exposure to sunlight, clothing habits and absence of sufficient amount of 25 (OH) vitamin D in most dietary sources in order to have the necessary amount required.

We found no correlation between 25 (OH) vitamin D level and different age groups probably because of the limited number of patients above 65 years.

25 (OH) vitamin D levels were not correlated to gender, as expected.

At baseline, there was no relationship between 25 (OH) vitamin D levels and other chemistry parameters such as corrected calcium, phosphorus, PTH. This is probably due to the small number of enrolled patients.

At baseline, 34 of the HD patients had a mean 25 (OH) vitamin D level of 19.3 ng/ml. After 6 months of cholecalciferol supplementation, there was a rise in the mean of 25 (OH) vitamin D to 27.9 ng/ml which represents a 45% increase from the baseline level (Fig. 1).

This increment is statistically significant, bringing the deficient patients closer to the recommended goal. Thus, the gap in the means of 25 (OH) vitamin D levels between the treated and non treated group was reduced.

Our data does not suggest safety concerns, because plasma calcium level did not change, therefore preventing other complications related to higher calcium levels. However, our data could not be conclusive due to the short period of time during which patients were treated. Concerning phosphorus, levels of HD patients increased from 4.8 mg/dl at baseline to 5.3 mg/dl at 6 months, with no statistical or clinical significance according to the new KDOQI guidelines. As for alkaline phosphatase levels, there was no statistically significance change at 6 months from baseline.

At 6 months, the non-treated group experienced 15% reduction in 25 (OH) vitamin D mean compared to the treated group that was noted to have 45% increase. This is important for vascular calcifications: London *et al*. reported an association between 25 (OH) vitamin D deficiency and vascular calcifications and pulse wave velocity in patients on maintenance HD [13]. At baseline, all HD patients had elevated PTH values: mean PTH value in the treated group was 397 pg/ml, compared to 351 pg/ml in the untreated group (Fig. 2). After 6 months of cholecalciferol supplementation, the treated group maintained its PTH value, while the untreated group developed an increase in PTH of 18% reaching a higher level than that of the treated group. These changes could be attributed to the increase in cholecalciferol level in the treated group which could have halted the rise of PTH (25 (OH) vitamin D mean increased 8 ng/ml in the treated group, while it decreased 5 ng/ml in the non-treated group). However, these changes were noted to be not statistically significant.

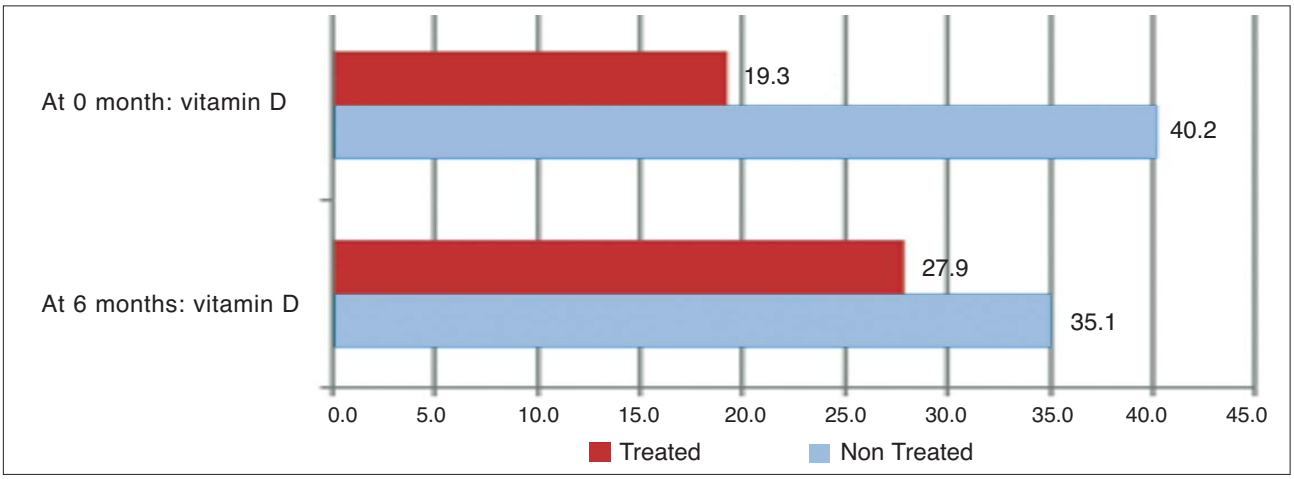

Figure 1. Difference in vitamin D levels between 0 and 6 months in the treated and non treated groups.

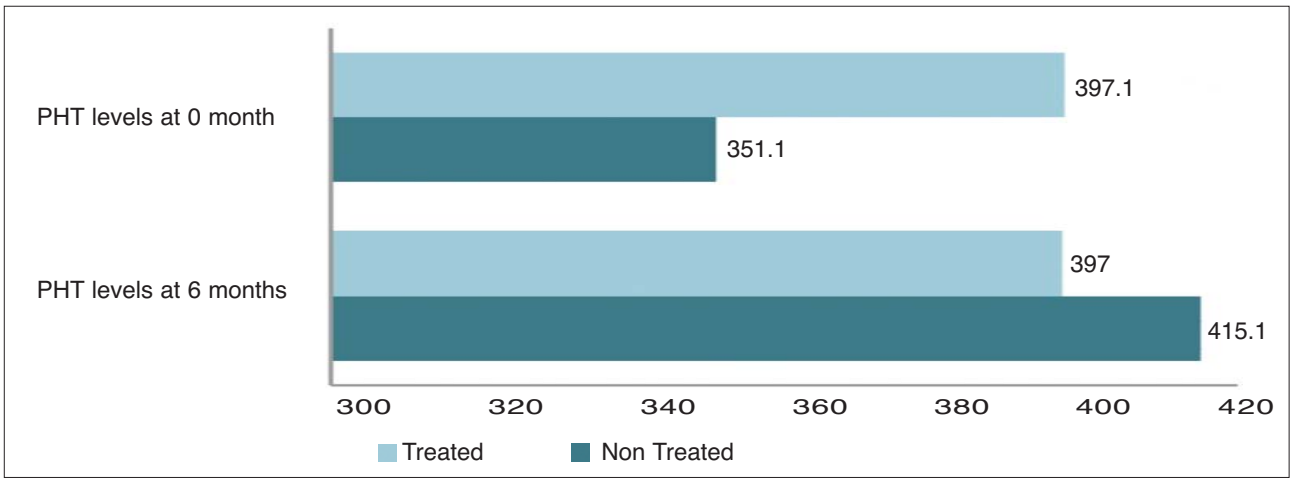

Figure 2. Difference in PTH levels between 0 and 6 months in the treated and non treated groups.

CONCLUSION

The sample studied in the general population showed high prevalence of 25 (OH) vitamin D deficiency (67%). The sample studied in HD patients showed a prevalence of 25 (OH) vitamin D deficiency of 32% and insufficiency of 36%.

Cholecalciferol supplementation safely improves vitamin D status and maintains PTH in 25 (OH) vitamin D deficient HD patients without increasing plasma calcium.

The pilot study showed that 25 (OH) vitamin D supplementation in the form of cholecalciferol is beneficial in HD patients.

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