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Original Research

The effects and safety of high dose vitamin D3 in hemodialysis patients

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Abstract

Background: Different studies have shown that hemodialysis patients require higher doses of Vitamin D3 (VD3) than the general population to achieve satisfactory replenishment. This study aims to assess the safety of such practice and its benefits on some of the parameters of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). **Methods:** A single-center clinical trial assessing the benefits of high dose VD3 in hemodialysis patients. The dose of VD3 (300,000 IU) was administered orally and monthly from April to December 2020 (9 months) at the dialysis unit. The data analyzed were blood levels of calcium, phosphorus, alkaline phosphatase, 25(OH)D, 1,25(OH)2D and intact parathyroid hormone (iPTH) done every three months. **Results:** We could recruit a cohort of 23 patients. Blood levels of 25(OH)D increased significantly in 82.6% of the patients to above 30 ng/ml. A similar effect was observed with 1, 25(OH)2D levels. iPTH levels decreased significantly when levels of 25(OH)D exceeded 30ng/ml at the end of the nine months. Vitamin D serum levels were typically measured immediately before the next monthly dose was administered. Blood levels of calcium, phosphorus, and alkaline phosphatase were stable during the study period. No events of hypercalcemia were reported, and no patient discontinued the monthly VD3 supplementation. **Conclusion:** Monthly administration of a high dose of VD3 over a long period of nine months in hemodialysis patients was found to be safe and beneficial in VD3 replenishment. It also allowed a significant decrease in iPTH levels. Further studies are warranted to identify the therapeutic target level of 25(OH)D in hemodialysis patients, allowing beneficial effects on iPTH.

Keywords: hemodialysis; secondary hyperparathyroidism; hypercalcemia; vitamin D3; parathyroid hormone

INTRODUCTION

It has been shown for long time that 25(OH)D deficiency is common in chronic kidney diseases patients. Its prevalence increases progressively with the loss of kidney function to reach above 90% of the patients at the dialysis stage.[1-4] Both deficiency and insufficiency (defined respectively as serum levels of 25(OH)D lower than 20 ng/mL and between 21–29 ng/mL) have been linked to many adverse clinical outcomes as well as high mortality and high cardiovascular morbidity rates in hemodialysis patients.[5-9] Levels above 30 ng/mL were advised for optimal health.[10,11] Despite this highly prevalent 25(OH)D deficiency, there is no clear guidelines regarding the optimal dose and strategy of administration of VD3. Different studies have shown that dialysis patients may require higher doses of VD3 than the general population to achieve adequate serum levels of 25(OH)D.[12,13] Using a single large dose of VD3 was shown to be more efficient in improving blood levels of 25(OH)D than the daily low dose.[14] On the other hand, an inverse relationship was shown to exist between iPTH and 25(OH)D.[10,11] However, the warranted effects on iPTH were mainly observed with higher doses of VD3.[10-12] We have noticed in our part of the world, a severe 25(OH)D deficiency in all the patients on dialysis in spite of the sunny weather all over the year.

We therefore undertook to prospectively study the outcome of a high dose of VD3 in our dialysis population. In order to assess its real impact, we opted to avoid patients on active VD and calcimimetics. The dose of the oral VD3 chosen was 300,000IU to be given monthly in the unit, post-dialysis for a better compliance. The elements assessed were the levels of calcium, phosphorus, alkaline phosphatase, 25(OH)D, 1,25(OH)$_2$D, and iPTH.

METHODS

Prospective clinical trial conducted at a single hemodialysis center. The cohort studied accepted and gave written consent to receive a monthly high dose of VD3 (300,000 IU orally at the end of the dialysis session). The aim of the study is to assess the safety of this large dose of VD3 and the effects on blood levels of calcium, phosphorus, alkaline phosphatase, 25(OH)D, 1,25(OH)2D and iPTH. These parameters were measured at the start of the study then every 3 months, immediately before the administration of the following monthly dose. Direct competitive chemiluminescent immunoassay (CLIA) method was used for the quantification of the above parameters. The study period chosen was nine months, from April to December 2020. The trial was registered in ISRCTN registry with a reference number; ISRCTN10043222.

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Patients

Patients included in the study were those above 18 years of age, with high iPTH, on regular hemodialysis for at least one year, and not on any active form of vitamin D or calcimimetics. All patients were dialyzed with a dialysis bath containing a calcium concentration of 1.50 mmol/l. We excluded patients with tertiary hyperparathyroidism or debilitating disease.

Data analysis

Data analysis was performed using Statistical Package for Social Sciences (IBM SPSS Statistics for Windows Version 26.0, IBM Corp. Armonk, NY, USA). One Continuous variable, such as patients' age and levels of clinical indicators of CKD-MBD, were described as means and standard deviations. In contrast, nominal and ordinal variables, such as sex, cause of CKD, and the number of years on hemodialysis treatment, were described using counts and frequencies. We defined outliers as values greater than 2.2 times the interquartile range from the lower or upper quartiles, 2, and were subsequently minorized. The clinical indicators of CKD-MBD levels at baseline, three months, six months, and nine months were tested for normality using the Shapiro-Wilk test and for sphericity using the Mauchly test of sphericity. All variables were found not to follow a normal distribution and/or have violated sphericity. Therefore, we used the Friedman test to test for significant differences among the levels of the clinical indicators or CKD-MBD at baseline, three months, six months, and nine months. Significance was set at $p<0.05$.

RESULTS

A cohort of 23 patients who responded to the inclusion criteria were selected. Males represented 52.2%, and the mean age was 72.8 years (SD=8.6). The cause of the initial renal disease was diabetes mellitus (78.3%), hypertension (17.4%) and unknown (4.3%). The majority of the patients were receiving 4 hours of dialysis per session and three sessions per week, and only 13% of the patients had two sessions per week. Most patients (91.6%) were on hemodialysis treatment from one year to less than 6 years, whereas (8.7%) of the patients were on hemodialysis for more than six years. The results of the parameters followed every three months are shown in Table 1. We observed a significant improvement of 25(OH)D levels at nine months (p <0.001). The levels of 1.25$(OH)_2$D also showed a significant increase (p <0.001). The levels of iPTH also exhibited a significant decrease at nine months (p<0.001). Table 2 shows that calcium, phosphorus, and alkaline phosphatase levels were stable for the whole study period. Not a single episode of hypercalcemia was noticed in our cohort, and therefore VD3 monthly supplementation has not been held for any patient. Table 3 shows that the majority of our patients (82.6%) reached levels of 25(OH)D above 30ng/ml, and none had levels below 20ng/ml.

DISCUSSION

The administration of large dose of vitamin D3 to our dialysis population over a long period (9 months) was found to be safe. It confirms the findings of others particularly those related to the stability of calcium and phosphorus levels.[15-17] We did not observe any episode of hypercalcemia during the whole study period. Furthermore, none of our patients exceeded 88 ng/ml, which could lead to complications.[18] The absence of recommendation of VD3 as part of the management of Secondary hyperparathyroidism (SHPT) is partly related to

Table 1. Blood levels of 25(OH)D, 1,25(OH)D and iPTH at baseline, 3,6 and 9 months (N=23)

		Mean ± S.D.				
Parameters	Baseline	3 months	6 months	9 months	X^2	P value
25(OH)D (ng/ml)	14.9 ± 5.2	21.4 ± 7.3	29.0 ± 8.0	39.6 ± 9.9	66.0	<0.001
1,25$(OH)_2$D (pg/ml)	10.5 ± 5.1	12.2 ± 4.5	17.8 ± 7.9	20.5 ± 9.8	37.6	<0.001
iPTH (pmol/l)	82.0 ± 46.1	80.5 ± 57.6	80.3 ± 56.2	53.2 ± 45.5	38.1	<0.001

Table 2. Blood levels of calcium, phosphorus, and alkaline phosphatase at baseline, 3,6 and 9 months (N=23)

		Mean ± S.D.				
Parameters	Baseline	3 months	6 months	9 months	X^2	P value
Serum Calcium (mmol/L)	2.1 ± 0.2	2.1 ± 0.2	2.1 ± 0.2	2.2 ± 0.2	7.8	0.051
Serum Phosphorus (mmol/L)	1.6 ± 0.5	1.6 ± 0.5	1.6 ± 0.5	1.6 ± 0.5	0.5	0.909
Alkaline Phosphatase (IU/L)	131.4 ± 63.4	133.7 ± 58.4	129.9 ± 53.1	145.1 ± 119.7	2.1	0.557

Table 3. Effect of large dose of vitamin D3 administration over 9 months on the levels of 25(OH)D

[25(OH)D]	0m (% of patients)	9m (% of patients)
< 20 ng/ml	78.3	0
20-30 ng/ml	8.7	17.4
> 30 ng/ml	13	82.6

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the fact that the effects of this supplementation on clinically relevant outcomes remain to be further defined.[19] On the other hand, the optimal dose and strategy of administration of VD3 and the 25(OH)D target serum level to decrease iPTH remain unanswered.[4,20] Different studies have shown that dialysis patients may require higher doses of VD3 than the general population to achieve adequate serum levels of 25(OH)D[13] and doses above 100,000 IU were suggested to be necessary to achieve adequate replenishment, increased $1,25(OH)_2D$, and decreased iPTH.[13,21]

One of the main topics of research in the field of SHPT, triggered by the inverse relationship between 25(OH)D and iPTH is to determine the target level of 25(OH)D beyond which an effect on the iPTH is observed. Levels of 25(OH)D between 42 and 48 ng/ml were judged more efficient therapeutic target without increasing calcemia or phosphatemia.[17] A recent study in CKD stages 3 and 4, using extended release calcifediol, showed that iPTH was significantly suppressed only when 25(OH)D levels were above 50.8 ng/ml. It also showed no significant changes in serum calcium and phosphorus levels in patients who reached 25(OH)D levels up to 92.5 ng/ml.[22] These findings suggest that the target level of 25(OH)D in CKD patients should be higher than the 30ng/ml recommended target for the general population. Indeed, in our cohort, we could observe a significant decrease in iPTH only when we reached the level of 39.6 ng/ml of 25(OH)D.

Vitamin D3, either from an exogenous or endogenous source, undergoes a double hydroxylation to be fully active. The first hydroxylation, in position 25, takes place in different tissues but mainly in the liver leading to 25(OH)D (also known as calcidiol or calcifediol). The second hydroxylation in position 1 leads to the active form $1,25(OH)_2D$ or calcitriol. It occurs mainly in the capillaries surrounding the proximal convoluted tubules, but other parts of the nephron (distal tubule and collector canal cells) also have this ability.[23,24] In the last two decades, many concepts regarding the physiology of VD3 have evolved, reinforcing the role of VD3 in the management of SHPT. Firstly, in physiologic conditions, the serum concentration of 25(OH)D is 1000 times more than 1,25(OH)2D, and its half-life is longer (25-30 days vs. 4-6 hours). Such facts would allow vitamin D status to be better reflected by the 25(OH)D serum level if we also consider that the liver hydroxylation is substrate-dependent and not regulated by negative feedback. Calcidiol can also activate Vitamin D Receptors (VDRs) and has a strong affinity to Vitamin D Binding Protein (DBP). All these characteristics suggest a physiologic role for 25(OH)D independent of $1,25(OH)_2D$. [24] Ravani and colleagues have shown that the level of 25(OH)D is a better risk marker than $1,25(OH)_2D$ in CKD. [2] Secondly, the concept that the kidneys were the only site where 1α hydroxylation has been challenged by the demonstration that other sites possess 1α hydroxylase (like bones, parathyroid cells, endothelial cells, vascular cells, and monocytes). Therefore, an autocrine pathway may generate $1,25(OH)_2D$ locally.[13,25,26] Moreover, 1α hydroxylase expression in parathyroid glands presumably suppresses the PTH gland hyperplasia in an autocrine/paracrine manner.[26] As 25(OH)D was an essential substrate for the local generation of 1, $25(OH)_2D$, the requirement for more 25(OH)D in these patients is warranted.[27,28] In SHPT, the expression of 1α-hydroxylase increases by ten folds, and the expression of 24 hydroxylase, which is responsible for the degradation of 25(OH)D and $1,25(OH)_2D$ decreases.[29] These elements may explain the inverse relationship between iPTH and 25(OH)D which was clearly shown to occur even in the earlier stages of CKD.[2,10,30,31] Our results are in line with the above findings as attested by the significant increase in the level of endogenous production of calcitriol. We may, therefore, easily understand the elegant option of using a high dose of cholecalciferol in the management of SHPT to obtain satisfactory endogenous calcitriol production without the side effects of exogenous calcitriol.[25] Indeed, although efficient in decreasing iPTH, exogenous calcitriol promotes hypercalcemia, hand vascular calcifications, and accelerated progression of aortic stiffness.[10]

As far as we know, our study is the first in our region to report the safe use of a large dose of VD3 in a cohort of hemodialysis patients. Similarly, to a few other reports, we noticed not only a satisfactory replenishment in 25(OH)D, but also a significant decrease in iPTH levels and a significant increase in $1,25(OH)_2D$.[17,32] Although encouraging, our study has limitations as our cohort is small and without a control group. The fact that our cohort is old and ethnically homogeneous, which reflects the typical dialysis population in our region may give some strength to our prospective study. The fact that the patients on active vitamin D and calcimimetics were excluded may have had assured that the results obtained were merely related to VD3. Interestingly, a recent study looked at the effect of cholecalciferol as an add-on to calcitriol and calcimimetics. It showed a further reduction in the levels of iPTH, an observation that provides additional evidence that inactive VD3 plays a role in controlling SHPT.[22] Therefore, we believe that adding calcimimetics to VD3, along with a more frequent administration of VD3 (weekly or bi-weekly) may be a better option for faster results.

CONCLUSION

In conclusion, our prospective study showed that the use of a large monthly dose of VD3 over long periods was safe, well-tolerated, and efficient. It had beneficial effect on the levels of iPTH and 1,25(OH)2VD. Further studies are highly warranted to verify these results and shed more light on the therapeutic target of 25(OH)D to reach, in order to obtain satisfactory levels of iPTH and 1,25(OH)2VD.

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CONFLICTS OF INTEREST

The authors certify that they have no affiliations with or involvement in any organization or entity with any financial or non-financial interest in the subject matter or materials

discussed in this manuscript

ETHICAL CONCERNS

Ethical approval was obtained from the University Hospital of Sharjah Research Ethical Committee (Reference: UHS-HERC-B042-161019). The study is registered in ISRCTN registry with a reference number; ISRCTN10043222.

DATA SHARING STATEMENT

The datasets generated during and/or analyzed during the current study will be available upon request from Dr Adnane Guella (adnane.guella@uhs.ae). Data will be available for 1 year from the date the study has ended by email. All the blood investigations studied can be available for sharing, as well as consent from participants.

AUTHOR'S CONTRIBUTION

AG and ARA contributed to the concept and design of the study. Both authors contributed to the data analysis. AG and ARA participated in the literature review and the writing of the manuscript and data interpretation. AG & MMH provided revisions to the scientific content and made a significant contribution to drafting the paper for its intellectual contribution. All authors contributed to critical revision and final approval of the manuscript and agreed to take responsibility for the manuscript's content.

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