Original Article

موضوع أصيل

VITAMIN D DEFICIENCY IN CHRONIC RENAL FAILURE HEMODIALYSIS PATIENTS

نقص الفيتامين D عند مرضى القصور الكلوي المزمن الخاضعين للتحال الدموي

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ملخص البحث

خلفية البحث: يعتبر نقص الفيتامين D من الأمور الشائعة لدى مرضى القصور الكلوي المزمن. يمتلك الفيتامين D تأثيراتٍ إيجابية على العظم والجهاز القلبي الوعائي وكذلك الوظائف المناعية. تم إجراء هذه الدراسة بغية تحديد مستوى الفيتامين D لدى مرضى القصور الكلوي المزمن الخاضعين للتحال الدموي.

طرق البحث: أجريت دراسة شاملة لتقييم مستوى الفيتامين D لدى 100 مريض في وحدة غسيل الكلية في مدينة الإمامين الكاظميين (ع) الطبية في بغداد، وتحديد العلاقة بين مستوى الفيتامين D ومختلف مؤشرات المرض باستخدام علاقة Pearson.

النتائج: بلغ معدل أعمار المرضى 51±16 سنة، 62% من المشاركين بالدراسة رجال و38% نساء، يعاني 36% منهم من الداء السكري. كانت مدة الخضوع للتحال الدموي أكثر من 6 أشهر، حيث خضع غالبية المرضى لثلاث جلسات غسيل في الأسبوع. بلغ معدل الفيتامين D 7.57±10.15 نانوغرام/مل. لوحظ لدى غالبية المرضى (بنسبة 97%) حالة نقص أو عدم كفاية في الفيتامين D، 92% بحالة عوز في الفيتامين D (مستوى الفيتامين دون 20 نانوغرام/مل)، منهم 59% بحالة نقص حاد (مستوى الفيتامين أقل من 10 نانوغرام/مل)، كما أن نسبة 5% من المرضى كانوا يعانون من عدم كفاية مستوى الفيتامين D (المستويات بين 20 و30 نانوغرام/مل). لوحظ لدى 3% فقط من المرضى مستويات طبيعية من الفيتامين D. بلغت معدلات مستويات الكالسيوم، الفوسفور، الفوسفاتاز القلوية والألبومين في المصل ما يلي على الترتيب 8.8±1.37 ملغ/دل، 5.0±1.47 ملغ/دل، 166.5±15 وحدة دولية/ل و3.6±0.56 غ/دل. بينما تراوحت قيم هرمون جارات الدرق PTH بين 17 و1928 بيكوغرام/مل بوسطي 296 بيكوغرام/مل. لم يلاحظ وجود علاقة بين مستوى الفيتامين D وكل من الوزن، الجنس، العمر، الألبومين، الفوسفور وهرمون جارات الدرق PTH.

الاستنتاجات: يعتبر العوز أو عدم الكفاية في الفيتامين D من الأمور الشائعة لدى مرضى التحال الدموي، مع وجود النقص الحاد في الفيتامين عند ثلثي المرضى المشاركين في هذه الدراسة.

ABSTRACT

Objective: *Vitamin D [(25(OH)D] deficiency and insufficiency is common in patients with chronic kidney disease (CKD). 25 (OH) D has been found to have beneficial effects on bone, cardiovascular and immune functions. This study was undertaken to determine the vitamin D status of CKD patients on hemodialysis.*

Methods: *We performed a cross-sectional study evaluating 25-hydroxy-vitamin D levels in 100 chronic dialysis patients in Al-Immamin Al-kadhimian city in Baghdad. Associations between vitamin D level and various disease markers were measured using Pearson correlation.*

Results: *The mean age of patients was 51±16 years, 62/100 (62%) were males and 38/100 (38%) were*

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females. 36/100 (36%) were diabetics. The duration of hemodialysis was more than 6 months. Most patients were on thrice weekly hemodialysis. The mean level of vitamin D was 10.15±7.57 ng/ml. Majority of the patients [97/100 (97%)] were either vitamin D deficient or had insufficient levels, and 92/100 (92%) were vitamin D deficient (levels <20 ng/ml); of these, 59/100 (59%) had severe vitamin D deficiency (levels <10 ng/ml) and 5/100 (5%) had insufficient levels (20-30 ng/ml) of vitamin D. Only 3/100 (3%) patients had normal levels of vitamin D. The mean levels of serum calcium, phosphorus, alkaline phosphatase, and albumin were 8.8±1.37 mg/dl, 5.0±1.47 mg/dl, 166.5±15 IU/l and 3.6±0.56 g/dl, respectively. PTH levels ranged from 17to 1928 pg/ml, and the median was 296 pg/ml. There was no significant correlation between 25 (OH)D levels and weight, sex, hemoglobin, age, alkaline phosphatase. Also, no correlations with albumin, phosphorus and PTH levels.

***Conclusions:** Vitamin D deficiency and insufficiency are universal in our hemodialysis patients, with severe vitamin D deficiency in two-third of patients.*

INTRODUCTION

New evidence has now established that the role of vitamin D is no longer solely restricted to its classical function of maintaining calcium and phosphate homeostasis. Vitamin D appears to play a more extensive role as a cell differentiating and anti-proliferative factor with actions in a variety of tissues, including the renal, cardiovascular, and immune.[1]

Patients with kidney disease have reduced activity of the enzyme 1-α hydroxylase (CYP27B1) in the kidneys, which converts 25-hydroxyvitamin D (25(OH) D) to its more active form 1,25-dihydroxyvitamin D ($1,25(OH)_2D$), and thus patients with kidney disease have traditionally been given vitamin D replacement with active, 1,25-dihydroxvitamin D or a related analog.[2]

As kidney function worsens, low circulating 1,25-dihyrdoxyvitamin D levels, low calcium levels, and high serum phosphate levels lead to secondary hyperparathyroidism (SHPT). SHPT, identified by elevated parathyroid hormone (PTH) levels, is associated with both bone disease (renal osteodystrophy) and, in epidemiologic studies, poor outcomes in dialysis patients.[3]

Multiple observational studies have shown low levels of both 25 (OH)D and 1,25 (OH)2D in patients with CKD and ESRD. Many factors may account for low levels of 25 (OH)D in kidney disease, including the loss of vitamin D binding protein in the urine, ineffective synthesis in the skin upon exposure to ultraviolet B radiation, and likely reduced nutritional intake and sun exposure.[4]

CKD is characterized by low 25 (OH) vitamin D (Calcidiol), low 1,25 $(OH)_2$ vitamin D (Calcitriol) as well as vitamin D resistance.[5] Alterations related to vitamin D metabolism, hyperphosphatemia and hypocalcemia lead to increased synthesis and/or secretion of PTH leading to secondary hyperparathyroidism, that sets in as soon as GFR falls below 60 ml/min.[6]

As early as stage 2 of CKD, serum 25 (OH) vitamin D levels begin to decline.[7] Reduced sun exposure, impaired skin synthesis of cholecalciferol due to renal disease, hyperpigmentation seen in late CKD stages and dietary restrictions that are commonly advised to CKD patients contribute to high prevalence of vitamin D deficiency.

In addition, uremia impairs intestinal absorption of dietary and supplemental vitamin D, and in CKD patients with severe proteinuria there are high urinary losses of vitamin D binding protein (DBP), leading to increased renal loss of vitamin D metabolites.[7,8]

Calcitriol binds to the intracellular vitamin D steroid receptor (VDR) to influence transcription of multiple genes across diverse target tissues. The traditionally understood, "classical" actions of Calcitriol are to increase gastrointestinal absorption of calcium and phosphate, thereby enhancing bone mineralization, and to suppress PTH secretion by the parathyroid glands. Calcitriol also influences transcription of "non-classical

" target genes in the kidney, heart and skeletal muscle, leukocytes, and pancreatic islets.[9]

Calcitriol potently inhibits renin expression through interaction of the VDR with response elements located within the promoter region of the renin gene, and moderates ventricular hypertrophy via direct effects on myocardial proliferation and contractility.[10]

Stimulation of the VDR also modulates expression of interleukins IL1, IL6 and tumor necrosis factor alpha by macrophages, and decreases expression of interleukin IL2 by lymphocytes.[11,12] These experimental findings are corroborated by observational studies in humans that demonstrate associations of lower 25-hydroxy and 1,25-dihydroxy vitamin D levels with higher blood pressure, inflammation, proteinuria, and diabetes.[11]

Recently published KDIGO (kidney disease, improving global outcomes) guidelines recommend that the serum 25 (OH) D level should be maintained over 30 ng/ml in patients of all stages of CKD.[12,13]

METHODS

The study was performed in Al-Nahrain College of Medicine in Al-Kadhimian Teaching Hospital in dialysis unit during the period of November 2014 to December 2015, 100 patients (62 males and 38 female) involved in this study of different age group ranging from (16 to 80) years (mean of age 51±16.4 years) complaining of chronic renal failure on regular hemodialysis. Each patient subjected to hemodialysis for period of 4 hours in two or three sessions per week, using GAMBRO AK95S haemodialysis apparatus with polyflux^{TM}L dialyzer membrane with effective surface area range from 1.4 to 2.1 m^2, and flow rate ranging from 250 to 300 ml/min. Patients on hemodialysis were required to have dialysis adequacy (Kt/v) of 1.2 or more.

All patients underwent a history and physical examination, we assess the vitamin D3 level among patients on hemodialysis in our center and virology screen, calcium, phosphorus, albumin, alkaline phosphatase, PTH and PCV, blood sample was collected before the hemodialysis sessions from vascular access. These samples was sent to the dialysis laboratory for analysis and measured in the same months.

Blood sample for 25 (OH) D was taken in a separate tube and centrifuge immediately and store in a cold storage (Roche Elecsys GmbH, sandofarstrasse 116, Germany). The patients were considered vitamin D insufficient if level between 20 and 30 ng/ml, and deficient if the levels less than 20 ng/ml. We also subcategorized these patients to severe deficiency if the level less than 10 ng/ml.

We included in our study the ESRD patients on hemodialysis those dialyzed for 4 hours and majority of them 2-3 times per week for six months and more. We excluded chronic kidney disease patients and the duration of hemodialysis less than 6 months.

Analytical method: Measurement of calcium and phosphorus, albumin, alkaline phosphatase by spectrometer method. These assays are done by Cobas C1, 11 Roche. 25 (OH)D level, serum parathyroid hormone PTH, virology screen by Cobas e4 11.

Statistical analysis: Data of 100 ESRD were transferred into computerized data based form and checked for error or inconsistency with aid of Microsoft excel 2007 (program for windows). Data management and statistical analysis were performed SPSS (statistical package for social science), version 23 for windows.

Descriptive statistic for continuous variables; age, weight, calcium level, PO4, albumin and vitamin D3 level, were presented as mean and standard deviation (SD), while categorical variables; sex, virology status, vitamin D categories (sufficient, insufficient, deficient) were presented as frequencies and percentage. Assess the correlation between 25(OH)D and various biochemical markers by Pearson method.

Chi-square used to assess the significance of association of vitamin D3 categories with other categorical variables. Level of significance was two

tailed and set at p-value less than 0.05 to be considered as significant.

RESULTS

One hundred hemodialysis patients were analyzed for their vitamin D status. The characteristics of these patients are as shown in Table 1. Mean age was 51±16.9 years. Of these, 38 were females and 62 were males, mean weight was 64.4±15.4 kg.

Characteristic of patients	Values
Male	62/100
Female	38/100
Hepatitis C positive	27/100 (27%)
Hepatitis B positive	2/100 (2%)
Hepatitis B, C positive	6/100 (6%)
Hepatitis (negative)	65/100 (65%)
Weight (in kg) (mean±SD)	64.4±15.4
Age (years) (mean±SD)	51±16.9

Table 1. Characteristics of patients.

In Table 2, mean packed cell volume (PCV) was 0.28±0.49 and albumin was 3.6±0.56 g/dl. Mean calcium, phosphorus, and alkaline phosphatase were 8.8±1.37 mg/dl, 5.0±1.47 mg/dl, and 166.5±15.0 IU/l, respectively. PTH levels ranged from 17 to 1928 pg/ml and the median was 296.0 pg/ ml.

Characteristics	Value
Albumin (mean±SD)	3.6±0.56
Calcium (mean±SD)	8.8±1.37
Phosphorus	5.0±1.47
Alkaline phosphatase	166.5 ±15.0
25 (OH)D	10.15±7.59
PTH	515.9±605.3
PCV (mean±SD)	0.28±0.49

Table 2. Biochemical characteristic of patients.

Table 3 shows the causes of chronic kidney disease. Thirty-two (36%) patients had diabetic nephropathy, and most patients were on thrice a week hemodialysis.

Mean 25 (OH)D level was 10.15±7.59 ng/ml. Only 3 (3%) patients were vitamin D sufficient and 5 (5%) were vitamin D insufficient. The remaining 33 (33%) were vitamin D deficient, Table 5. Of these, 59 (59%) had severe vitamin D deficiency with 25 (OH)D less than 10 ng/ml. Majority of these patients were on usual calcium supplements.

Causes	Frequency
Diabetes	36/100 (36%)
Hypertension	32/100 (32%)
Polycystic kidney disease	6/100 (6%)
Obstruction	6/100 (6%)
Glomerulonephritis	7/100 (7%)
Pyelonephritis	8/100 (8%)
Unknown	5/100 (5%)

Table 3. Causes of chronic kidney disease.

There was no significant correlations between 25 (OH)D levels and weight, sex, PCV, age, alkaline phosphatase, and also, no correlation with PTH levels, phosphorus and albumin, Table 6.

DISCUSSION

Vitamin D deficiency, insufficiency and sufficiency were seen in 92%, 5% and 3% respectively, of our patients on hemodialysis as compared to vitamin D level in normal population were 52.8%, 37.7% and 9.4% respectively in Al-Jebouri et al study from Tikrit government in our country.[14]

Vitamin D	DM	HTN	PCKD	Obstruction	GN	PN	Unknown	Total
Sufficient	0	2	0	0	0	1	0	3
Insufficient	3	2	0	1	0	1	0	7
Deficient	9	9	3	0	3	4	3	31
Severe deficient	24	19	3	5	4	2	2	59

Table 4. Shows the relation between sub-categorized of vitamin D and the cause of CKD and p-value was 0.56.

The mean vitamin D was 10.15±7.59 ng/ml in our patients on hemodialysis as compared to 31.42±2.98 ng/ml, in normal adult population in Al-Jebouri et al study. Severe deficienc y was also very common, with as many as 59% patients showing serum 25 (OH)D values below 10 ng/ml.

Vitamin D status	No.
Severe vitamin D deficiency (<10 ng/ml)	59/100
Vitamin D deficient (10-20 ng/ml)	33/100
Vitamin D insufficient (21-30 ng/ml)	5/100
Vitamin D sufficient (>30 ng/ml)	3/100

Table 5. Vitamin D status of the patients.

Parameter	Correlation coefficient	p-value
Age	-0.17	0.08
Weight	0.34	0.7
Sex	0.16	0.11
Calcium	0.14	0.13
Phosphorus	0.07	0.51
Albumin	0.09	0.4
Alkaline phosphatase	-0.13	0.18
PTH	-0.06	0.54
PCV	0.28	0.7

*PTH=parathyroid hormone, PCV=packed cell volume

Table 6. The correlation between 25 (OH) D level and various clinical and biochemical parameters.

Our findings are compared with previous data from Chandigarh which reported 77% prevalence of vitamin D deficiency, and 22% insufficiency in male patients with newly diagnosed CKD patients.[15]

In Bhan I et al study[16] from North America, the result of vitamin deficiency, insufficiency and sufficiency were 20%, 77% and 3% of patients on hemodialysis respectively. In Beena Bansal et al study[17] from North India were 64.4%, 31.8% and 4.4% of patients respectively. Of note, most of these patients were on calcium carbonate preparations two to three times a day. We found that 25 (OH)D levels were low in most patients.

We found in our study; there is no significant correlation between the age, sex, PCV, calcium, albumin, alkaline phosphatase and weight with vitamin D levels.

Also, presence of diabetes was not correlated with vitamin D levels, while in a previous study (Bhan I), the female sex and hypoalbuminemia were found to be correlated with vitamin D deficiency in hemodialysis patients.

Also, the correlation of vitamin D levels with presence of diabetes is interesting. There is evidence of effect of vitamin D deficiency on glucose metabolism, but vitamin D deficiency being more common in CKD patients with diabetic nephropathy as the basic disease is not commonly reported.[16]

We did not find any correlation between PTH levels and 25 (OH)D, although an inverse correlation has been shown in previous studies (Chandigarh) which were done in earlier stages of CKD (Stages 3 and 4).[15]

CONCLUSIONS

In this cross-sectional study, vitamin D insufficiency or deficiency was found to be highly prevalent in chronic dialysis patients. Although vitamin D deficiency was highly prevalent in our dialysis patients, we were unable to demonstrate a correlation between a 25-hydroxy-vitamin D level and the majority of disease markers evaluated in this study. Further research is necessary to fully elucidate the consequence of vitamin D deficiency in patients with end-stage renal disease. They probably require routine supplementation with higher doses of cholecalciferol. Further studies on supplementation are being carried out to define optimum dose schedules.

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