The effects of cholecalciferol treatment on mineral metabolism and inflammation markers in Turkish hemodialysis patients

Sultan Ozkurt, MD, Ahmet Musmul, PhD.

ABSTRACT

الأهداف: تقييم آثار هدروكسي كوليكالسيفرول على الأيض ومؤشرات الالتهاب في المرضى الخاضعين لغسيل الكلى.

الطريقة: أجريت الدراسة في جامعة هتيت، كروم، تركيا خلال الفترة من يوليو حتى سبتمبر 2012م. من بين 36 مريض كان هنالك 28 مريض مستوى فيتامين د لديهم أقل من 30 نانوغرام/مل متوسط العمر (18±52) عام. اشتملت الدراسة على 15 ذكر، و13 أنثى. تم علاج المرضى الذين يصل مستوى فيتامين د أقل من 30 نانغرام/مل بجرعة تبلغ 20,000 وحدة عالمية مرة يومياً ولمدة 12 أسبوع. تم تقييم مستوى هدروكسي كوليكالسيفرول، وعلامات الاستقلاب للمعدن، وبروتين التفاعل.

النتائج: بعد العلاج ارتفعت مستويات فيتامين د لتصل إلى أكثر من 30 نانوغرام/مل لجميع المرضى 12.5±7.1 نانوغرام/مل بالمقابل 59.9±15.5 نانوغرام/مل، (p<0.001). سجل ارتفاع إحصائي مهم وغير مهدد للحياة لمستويات الكالسيوم 7.9 (7.26 إلى8.32) نانوغرام/مل بالمقابل 8.48 (7.55 إلى 9.25)، p<0.001. كما سجل انخفاض إحصائي في مستوياتCRP بينما لم يظهر هنالك أي اختلاف في مستويات الغدة الدرقية، والفسفور، والفوسفات.

خاتمة: يعد نقص فيتامين د مشكلة منتشرة في المرضى الخاضعين للغسيل الدموي. أن العلاج باستخدام هيدركوكسي كولسيرون يعد آمن وفعال في مجموعة المرضى وله تأثير ايجابي لأعراض الالتهاب.

Objectives: To evaluate the effects of 25-hydroxycholecalciferol (25-[OH] D) on bone mineral metabolism and inflammation parameters in hemodialysis patients.

Methods: The study was carried out at Hitit University Corum Education and Research Hospital, Corum, Turkey between July and September 2012. All of the 36 patients that underwent treatment in our hemodialysis unit were included in this study. Four patients were excluded from the study due to other complications. Of the remaining 32 patients, 28 patients (mean age; 52 ± 18 years; 15 males and 13 females) with a 25-(OH) vitamin D level of <30 ng/mL were included in the study. Four of the 32 remaining patients were excluded as their 25-(OH) vitamin D levels was >30 ng/ml. Patients with a 25-(OH) D level of <30 ng/mL were treated with 20,000 IU oral cholecalciferol once a week for 12 weeks. The level of vitamin D, mineral metabolism markers, and C-reactive protein (CRP) were evaluated.

Results: After the treatment, the 25-(OH) D levels increased to >30 ng/mL in all patients (12.5±7.1 ng/mL versus 59.9±15.5 ng/mL; p<0.001). While there was a significant, but not life-threatening, increase in calcium levels (7.9 [7.26 to 8.32] mg/dL versus 8.48 [7.55 to 9.25] mg/dL, p<0.001), a statistically significant decrease was observed in CRP levels (9.34±4.4mg/L versus 4.4±1.6mg/L; p<0.001). Alkaline phosphatase, phosphorus, and parathyroid hormone levels did not change.

Conclusion: Vitamin D deficiency is a common problem in HD patients. Short-term weekly cholecalciferol treatment is safe and effective in this patient group, and cholecalciferol treatment had a positive effect on inflammatory markers.

Saudi Med J 2013; Vol. 34 (5): 497-502

From the Department of Nephrology (Ozkurt), Hitit University Corum Education and Research Hospital, Corum, and the Department of Statistics (Musmul), Faculty of Medicine, Eskisehir Osmangazi University, Eskisehir, Turkey.

Received 18th February 2013. Accepted 28th April 2013.

Address correspondence and reprint request to: Dr. Sultan Ozkurt, Department of Nephrology, Division of Nephrology, Hitit University Corum Education and Research Hospital, Çorum 19100, Turkey. Tel. +90 5058614870. Fax. +90 3642230323. E-mail: dr.s.guvenir@hotmail.com/amusmul@ogu.edu.tr

Patients with chronic renal failure often have 25-hydroxycholecalciferol (25-[OH] D) (calcidiol) deficiency, which is the substrate of 1,25-dihydroxy-vitamin D (calcitriol). As the chronic kidney disease progresses, the vitamin D substrate and renal 1-α-hydroxylase deficiency cause progressive calcitriol deficiency.[1,2] With recent evidence demonstrating extrarenal 1-α-hydroxylase expression in many tissues other than the kidney, measurement of 25-(OH) vitamin D level has gained importance.[3] It has been suggested that anephric patients have extrarenal 1 alpha, 25- dihydroxyvitamin D (1,25-[OH] 2D) production,[4] and that calcitriol levels increase with 6 months of 25-(OH) vitamin D replacement therapy in hemodialysis (HD) patients.[5] The major circulating form of vitamin D is 25-(OH) D, and serum levels of vitamin D in the body reflect the level of storage. The 25-(OH) vitamin D levels are recommended to be >30 ng/mL in the general population and in stage 3-4 chronic kidney disease (CKD) patients. The Kidney Disease Outcomes Quality Initiative guidelines (K/DOQI) provide recommendations for vitamin D repletion only to patient with stage 3 and 4 CKD who have 25-(OH) D concentrations <30 ng/ml.[6] This regimen is generally a variation on 50,000 IU vitamin D/week for a period of 6-12 weeks. This treatment regimen is inexpensive and reliable with fewer side effects, and it provides physiological vitamin D replacement.[6] There is a limited number of studies on the optimal dose and duration of this treatment regimen that supports the use of this regimen in hemodialysis patients, and it is not yet included in the K/DOQI guidelines.[6,7] However, the extraskeletal effects of vitamin D are included in the Kidney Disease Improving Global Outcomes guidelines (K/DIGO) and it has been recommended that CKD stage 3-5 patients should be evaluated by the measurement of 25-(OH) D levels and those with vitamin D deficiency should be treated similar to the general population.[8] A large number of studies have shown many positive effects of vitamin D therapy (active vitamin D and vitamin D analogs), particularly on calcium-phosphorus homeostasis, in HD patients.[9-11] Vitamin D, particularly active vitamin D, has been shown to affect the gene expression in many tissues.[11] Local calcitriol is produced by 1-α-hydroxylase, is involved in cell differentiation, and acts as an antiproliferative agent.[11] In a recent prospective cohort study,[12] vitamin D deficiency was reported to be associated with high mortality rates in HD patients, and has been suggested to be a risk factor for cardiovascular diseases in patients with chronic renal failure.[13] In a multicenter and prospective randomized study, Kendrick et al[14] found that low 1,25-(OH)2 vitamin D levels were associated with mortality and progression to long-term dialysis therapy in patients with advanced stage chronic renal failure who are not yet on dialysis.[14] In the present study, we aimed to determine the 25-(OH) vitamin D level in a Turkish hemodialysis patient population, to evaluate the effectiveness of 12 weeks of weekly 25-(OH) vitamin D treatment (20,000 IU) in this patient population, and to evaluate the effects of this treatment regimen on bone mineral metabolism and parameters of inflammation.

Disclosure. The authors have no conflict of interests, and the work was not supported or funded by any drug company.

Methods. This study was carried out at Hitit University Corum Education and Research Hospital, Corum, Turkey between July and September 2012. This was a cross-sectional study, and a total of 36 HD patients were recruited among the patients who were receiving treatment in the Dialysis Unit of the hospital and were receiving our standardized HD prescriptions (500 mL/min dialysate flow: 200-250 mL/min blood flow; 4 hours per session of dialysis, 3 sessions per week). Subjects had been on maintenance dialysis for an average of 4 years. The exclusion criteria were current or previous treatment with cinacalcet, previous parathyroidectomy, serious secondary hyperparathyroidism (iPTH >600 pg/mL), hypercalcemia (Ca >10.2 mg/dL), hyperphosphatemia (*p*>5.5 mg/dL), and current acute or chronic infection, or systemic disease that can cause inflammation. Two patients were excluded from the study due to severe secondary hyperparathyroidism, one patient due to chronic liver disease, and one patient due to hyperphosphatemia. Of the remaining 32 patients, 28 patients (mean age 52 ± 18 years; 15 males and 13 females) with a 25-(OH) vitamin D level of <30 ng/mL were included in the study (since 4 of the 32 remaining patients had 25-(OH) vitamin D levels of >30 ng/ml, they were not included in the study). The patients received stable doses of calcitriol and paricalcitol during the study period, and the dose of phosphorus-binding drugs were not changed. In addition, 1.25 mmol/L Ca dialysate was used.

All the patients'medical records since the beginning of dialysis were reviewed for clinical history, laboratory parameters, and medications. Arterial blood pressure was measured at least twice in the morning after a

15-minutes resting interval as mean values of systolic (SBP) and diastolic (DBP) pressure, and the average of the 2 measurements was calculated. The SBP and DBP values, blood urea nitrogen (BUN), serum creatinine, albumin, hemoglobin, calcium (Ca), phosphorus (P), uric acid, intact parathyroid hormone (iPTH), and C-reactive protein (CRP) levels were measured. Blood samples were obtained in the morning after an overnight fasting period (before starting a dialysis session in HD patients). Routine serum biochemical variables including Ca, P, albumin, uric acid, and hemoglobin were analyzed using standard laboratory methods. Serum iPTH levels were measured by electro chemiluminescence immunoassay (Moduler Analytics E 170/ Roche Diagnostic, Tokyo, Japan). Serum CRP levels were measured by the nephelometric method (SEAC-RADIM, DELTA, Florence, Italy). The normal range for CRP is 0-8 mg/L. The 25-(OH) D level was measured by the high-performance liquid chromatography (HPLC) method (Shimadzu Corporation, Kyoto, Japan) using a commercially available kit (ImmuChrom, Heppenheim/Hessen, Germany). Informed consent was taken from all participants. This study was approved by the Medical Ethics Committee of Erciyes University, and was conducted in compliance with the recommendations of the Declaration of Helsinki on Biomedical Research Involving Human Subjects. The patients with 25-(OH) D levels of <30 ng/ml received oral 20,000 IU of cholecalciferol (Devit-3 Oral Damla, DEVA Pharmacy, Istanbul, Turkey) once a week after the dialysis for 12 weeks under the supervision of dialysis nurses. All parameters were re-examined after 12 weeks of treatment.

Statistical analyses. All data analyses were performed by using IBM PASW (Predictive Analics SoftWare Statistics) version 18, (SPSS Inc., Chicago, IL, USA). Normally distributed variables were summarized with n (sample size), mean, and standard deviation, and non-normally distributed variables were summarized with n (sample size), median, 25th, and 75th percentiles. Normally distributed variables were compared before and after treatment by the paired t-test. Non-normally distributed variables were compared before and after treatment by the Wilcoxon signed-rank test. A p-value less than 0.05 ($p<0.05$) was accepted as significant.

Results. The mean duration of dialysis was 54 (range, 12-240) months. The mean body mass index (BMI) was 24±5 kg/m^2, SBP was 129±23 mm Hg, DBP was 74±11 mm Hg, laboratory indicators of dialysis dosage (Kt/V) was 1.42 (range, 1.36 to 1.62), and urea reduction ratio (URR) was 71±6. In 28 of 32 patients (87.5%), 25-(OH) D level was <30 ng/mL. Of the 28 patients, vitamin D insufficiency (20-30 ng/mL) was found in 3 (10.7%), mild deficiency (10-20 ng/mL) in 10 (35.7%), and severe deficiency (<10 ng/mL) in 15 (53.57%) patients. For the treatment of secondary hyperparathyroidism, 10 patients (35.7%) were receiving calcitriol, 2 patients (7.1%) were receiving paricalcitol, and 25 patients (89.3%) were receiving calcium acetate. Of the patients, 8 (28.5%) had a diagnosis of diabetes mellitus, and 21 (75%) had a diagnosis of hypertension. All the 21 hypertensive patients were taking antihypertensive medication. There were no patients using antilipemic drugs. Twenty-six patients were using recombinant erythropoietin to maintain their predialysis hemoglobin level at 11-12 g/dL. The etiology of the chronic renal failure was diabetes mellitus in 8 patients, hypertension in 6 patients, renal stone disease in 4 patients, glomerulonephritis in 3 patients, polycystic kidney disease in 2 patients, and renal vein thrombosis in one patient, while the etiologic factor was unknown in 4 patients. **Table 1** summarizes the subjects' demographics.

After 12 weeks of treatment, the 25-(OH) D level increased to >30 ng/mL in all patients (12.5±7.1 ng/mL versus 59.9±15.5 ng/mL, $p<0.001$). There was a statistically significant decrease in CRP (9.34 ± 4.4 mg/L versus 4.4±1.6 mg/L, $p<0.001$). After the cholecalciferol treatment, hemoglobin, alkaline phosphatase, phosphorus, and iPTH levels did not change significantly, while there was a significant, but not life-threatening increase in Ca and Ca×P levels (7.9 [7.26-8.32] mg/dL versus 8.48 [7.55-9.25] mg/dL, $p<0.001$, and 36.57±7.88 versus 39.56±10.61, $p=0.038$). The Ca level did not exceed the level of 10.5 mg/dL in any of the patients. In addition, the serum albumin level increased significantly after treatment (3.51±0.42 g/dL versus 3.89±0.46 g/dL, $p<0.001$); however, uric acid

Table 1 - Subject characteristics by treatment group in patients included in a study at Hitit University Corum Education and Research Hospital, Corum, Turkey.

Characteristics	Treatment group (n=28)
Gender (male/female)	15/13
Age (years)	52±18
Body mass index (Kg/m^2)	24±5
Duration of dialysis (months)	54 (12-240)
Diabetes mellitus/hypertension	8/21
Calcitriol/paricalcitol treatment	10/2
Calcium acetate treatment (%)	25 (89.3)
Kt / V	1.42 (1.36-1.62)

Kt / V - laboratory indicators of dialysis dosage

Table 2 - Laboratory parameters before and after 12 weeks of cholecalciferol supplementation.

Parameter	Before treatment (n=28)	After treatment (n=28)	95% Confidence interval of the mean difference		*P*-value
			Lower	Upper	
Hemoglobin,* g/dl	10.46 ± 1.57	10.64 ± 1.54	-0.784	0.434	0.560
Blood urea nitrogen,* mg/dl	68.39 ± 18.28	67.61 ± 12.16	-5.131	6.690	0.789
Creatinine,* mg/dl	8.65 ± 3.19	8.45 ± 2.88	-0.270	0.660	0.397
Albumin,* g/dl	3.51 ± 0.42	3.89 ± 0.46	-0.528	-0.236	<0.001
C-reactive protein,* mg/L	9.35 ± 4.44	4.44 ± 1.61	3.278	6.530	<0.001
25- hydroxyvitamin,* D ng/ml	12.52 ± 7.08	59.99 ± 15.53	-53.396	-41.542	<0.001
Calcium,† mg/dl	7.90 (7.26-8.32)	8.48 (7.55-9.25)	-	-	<0.001
Phosphorus,† mg/dl	4.95 (3.92-5.5)	5.00 (4.5-5.5)	-	-	0.871
Ca x P*	36.57 ± 7.88	39.56 ± 10.61	-5.790	-0.180	0.038
Corrected Ca,† mg/dl	8.3 (7.49-8.74)	8.52 (7.6-9.14)	-	-	0.017
Alkaline phosphatase,† U/L	100 (69-165)	100.5 (69-223)	-	-	0.079
Uric acid,* mg/dl	6.98 ± 1.12	6.49 ± 1.21	0.0973	0.888	0.016
iPTH,† pg/ml	345.50 (125.5-600)	340.60 (113.4-600.5)	-	-	0.732

Values are given as mean (SD) or median (range). *t-test, mean (SD), †Wilcoxon signed-rank test, median (Q1-Q3), Ca - calcium, P - phosphorus, iPTH - intact parathyroid hormone

levels were significantly decreased after the treatment (6.99±1.12 mg/dL versus 6.49±1.21 mg/dL, p=0.016) (**Table 2**).

Discussion. Our results indicate that despite allowing the fixed dose of active vitamin D and paricalcitol treatments during the study period, a high proportion of hemodialysis patients had 25-(OH) vitamin D deficiency, and that treatment with cholecalciferol increased the 25-(OH) vitamin D to desired levels in all patients without any evidence of significant toxicity. Some studies have reported the results of weekly short-term,[15] and monthly long-term,[16] outcomes of cholecalciferol treatment; however, there is no direct data indicating the best regimen for HD patients.

Recently, rapid correction of vitamin D deficiency in patients with end-stage renal failure with high-dose treatments is becoming popular, and there are a limited number of studies regarding this issue in HD patients. Among the studies using a dose below 50,000 IU, previous studies[17,18] treated patients for 9 months (20,000 IU/week) and 24 months (40,000 IU/month) and the ratio of increasing vitamin D to the desired level (>30 ng/mL) was found to be 57% and 77%. In the studies using 50,000 IU or more vitamin D for relatively longer durations (6 months or more), the treatment has been shown to be effective (15 month [100,000 IU/month], 24 weeks [50,000 IU once a week for the first 12 weeks, and 20,000 IU in the last 12 week of the study], and 6 months [50,000 IU/week for patients with 25-(OH) D<15 ng/ml, 10,000 IU/week when 25-(OH) D was between 16 and 30 ng/ml, and 2700 IU 3 times per week when 25-(OH) D levels where >30ng/ml]).[16,19,20] Furthermore, a study using very high doses of vitamin D (200,000 IU/week) for a short duration (3 weeks) found the treatment regimen to be effective with no signs of vitamin D toxicity.[13] In our study, we used a relatively low dose of vitamin D and a short-term treatment regimen in order to facilitate patient compliance and to prevent potential adverse effects of high doses of vitamin D. The prevalence of vitamin D insufficiency and deficiency in HD patients is estimated to be between 78- 91%.[12,21-23] In our study, 87% of the patients had a vitamin D level of <30 ng/mL and approximately half (53.5%) had severe vitamin D deficiency. Because we gave the cholecalciferol supplementation in the summer, the treatment was not considered to be affected by the seasonal change in sunlight exposure. However, the vitamin D insufficiency in HD patients might be explained partly by poor dietary intake and inadequate sunlight exposure due to the facts that majority of the bodies of the patients (except hands and head) was covered, and they spent most of their time indoors. After the treatment, all of the patients reached desired levels of vitamin D (>30 ng/mL) without signs of toxicity. Although we used a short-term treatment with a dose of 20,000 IU/week, compared with the previous studies using higher doses and longer-term studies, we achieved the desired target in all of our patients. This may be attributed to the fact that (i) the drugs were administered by dialysis nurses and compliance of the patients was good, (ii) there were no conditions causing inadequate response such as obesity, liver disease, or impaired intestinal absorption, (iii) the treatment was given in the summer months when

sunlight exposure was maximized, and (iv) the baseline 25-(OH) vitamin D level was not too low. Treatment with vitamin D is associated with concerns regarding hypercalcemia, hyperphosphatemia, and adynamic bone disease; however, phosphorus, PTH, and ALP levels remained unchanged. There was a significant, but not life-threatening increase in Ca and Ca×P levels and Ca levels remaining between desired values. There are inconsistent study results related to replacement therapy with vitamin D2 or vitamin D3 in hemodialysis patients. Some studies have reported a significant decrease in PTH levels,[5,16,19] while others have found no significant change.[17,20,24,25] In light of these results, it seems to be impossible to expect an effective treatment for secondary hyperparathyroidism with cholecalciferol treatment in HD patients. Various studies have suggested the existence of non-classic effects of vitamin D including maintaining innate immunity, anti-atherosclerotic effect, and normalization of inflammatory reaction.[3,26,28] Association between vitamin D deficiency and systemic inflammation was identified in experimental studies. Calcitriol may decrease the expression of IL-6, IL-1, and interferon gamma, and cause the upregulation of IL-10, which is an anti-inflammatory cytokine.[28,29] Systemic inflammation is often seen in dialysis patients, and it is a significant predictor of mortality in this population.[30] Although there are multiple causes for the existence of inflammation, hypovitaminosis D may be an unrecognized and a potentially reversible cause for this situation. Our study, like other studies,[19,20] indicates a reduction in the inflammatory parameters, with an increase in albumin, and a reduction in CRP. This could reflect the anti-inflammatory effect of cholecalciferol, and could potentially represent a new therapeutic opportunity to reduce systemic inflammation and mortality in CKD HD patients. However, after effective treatment of 25-(OH) vitamin D deficiency in HD patients, Jean et al[16] found a significant increase in albumin levels, but no change in CRP levels. Accordingly, in another study by Jean et al,[22] no significant change in albumin and CRP levels had been reported and finally, Markman et al[25] also reported no change in IL-6 and CRP levels. Because of these conflicting results, a large number of randomized controlled studies are needed to clearly suggest pleiotropic effects of cholecalciferol treatment in HD patients. Forman et al[31] suggested that 25-(OH) vitamin D deficiency is associated with the development of hypertension and an increase in uric acid. Conversely, although the underlying mechanism is unknown, uric acid levels significantly decreased after the cholecalciferol treatment in our study. The relationship between increased uric acid levels and coronary artery disease has been shown in several studies, and D'Marco et al[32] suggested that a uric acid level of >6 mg/dL is associated with an increased risk of calcification and cardiovascular events in patients with chronic renal insufficiency undergoing dialysis. Thus, one may suggest that the effects of 25-(OH) vitamin D treatment on uric acid levels may contribute to cardiovascular protection.

The limitations of this study include that this study is a non-randomized uncontrolled design, and that we did not measure 1,25-dihydroxyvitamin D levels.

In conclusion, vitamin D deficiency is a common problem in Turkish hemodialysis patients. A short-term weekly cholecalciferol treatment regimen is safe and effective in this group of patients. According to the results of our study, inflammatory markers were reduced by treatment of cholecalciferol but large, long-period, randomized and controlled studies are needed for detecting the effect of this treatment on mortality and morbidity.

References

1. Goodman WG, Coburn JW. The use of 1,25-dihydroxyvitamin D3 in early renal failure. ***Annu Rev Med*** 1992; 43: 227-237.
2. Schroeder NJ, Cunningham J. What's new in vitamin D for the nephrologist? ***Nephrol Dial Transplant*** 2000; 15: 460-466.
3. Jones G. Expanding role for vitamin D in chronic kidney disease: Importance of blood 25-OH-D levels and extra-renal 1α-hydroxylase in the classical and non-classical actions of 1α,25-dihydroxyvitamin D3. ***Semin Dial*** 2007; 20: 316-24.
4. Lambert PW, Stern PH, Avioli RC, Brackett NC, Turner RT, Greene A, et al. Evidence for extrarenal production of 1 alpha, 25-dihydroxyvitamin D in man. ***J Clin Invest*** 1982; 69: 722-725.
5. Jean G, Terrat JC, Vanel T, Hurot JM, Lorriaux C, Mayor B, et al. Evidence for persistent vitamin d 1-alpha-hydroxylation in hemodialysis patients: Evolution of serum 1,25-dihydroxycholecalciferol after 6 months of 25-hydroxycholecalciferol treatment. ***Nephron Clin Pract*** 2008; 110: 58-65.
6. K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. ***Am J Kidney Dis*** 2003; 42: 1-201.
7. 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*** 2009; 76: S1-S130.
8. Hollis BW. Circulating 25-hydroxyvitamin D levels indicative of vitamin D sufficiency: implications for establishing a new effective dietary intake recommendation for vitamin D. ***J Nutr*** 2005; 135: 317-322.
9. Teng M, Wolf M, Lowrie E, Ofsthun N, Lazarus JM, Thadhani R. Survival of patients undergoing hemodialysis with paricalcitol or calcitriol therapy. ***N Engl J Med*** 2003; 349: 446-456.

10. Tentori F, Hunt WC, Stidley CA, Rohrscheib MR, Bedrick EJ, Meyer KB, et al. Mortality risk among hemodialysis patients receiving different vitamin D analogs. ***Kidney Int*** 2006; 70: 1858-1865.
11. Gurlek A, Pittelkow MR, Kumar R. Modulation of growth factor/cytokine synthesis and signaling by 1-alpha,25-dihydroxyvitamin D(3): implications in cell growth and differentiation. ***Endocr Rev*** 2002; 3: 763-786.
12. Wolf M, Shah A, Gutierrez O, Ankers E, Monroy M, Tamez H, et al. Vitamin D levels and early mortality among incident hemodialysis patients. ***Kidney Int*** 2007; 72: 1004-1013.
13. Levin A, Li YC. Vitamin D and its analogues: do they protect against cardiovascular disease in patients with kidney disease? ***Kidney Int*** 2005; 68: 1973-1981.
14. Kendrick J, Cheung AK, Kaufman JS, Greene T, Roberts WL, Smits G, et al. Associations of plasma 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D concentrations with death and progression to maintenance dialysis in patients with advanced kidney disease. ***Am J Kidney Dis*** 2012; 60: 567-575.
15. Wasse H, Huang R, Long Q, Singapuri S, Raggi P, Tangpricha V. Efficacy and safety of a short course of very-high-dose cholecalciferol in hemodialysis. ***Am J Clin Nutr*** 2012; 95: 522-528.
16. Jean G, Souberbielle JC, Chazot C. Monthly cholecalciferol administration in hemodialysis patients: a simple and efficient strategy for vitamin D supplementation. ***Nephrol Dial Transplant*** 2009; 24: 3799-3805.
17. Tokmak F, Quack I, Schieren G, Sellin L, Rattensperger D, Holland-Letz TG, et al. High-dose cholecalciferol to correct vitamin D deficiency in haemodialysis patients. ***Nephrol Dial Transplant*** 2008; 23: 4016-4020.
18. Jakopin E, Pecovnik Balon B, Ekart R, Gorenjak M. High-dose cholecalciferol supplementation for vitamin D deficiency in haemodialysis patients. ***J Int Med Res*** 2011; 39: 1099-1106.
19. Matias PJ, Jorge C, Ferreira C, Borges M, Aires I, Amaral T, et al. Cholecalciferol supplementation in hemodialysis patients: effects on mineral metabolism, inflammation, and cardiac dimension parameters. ***Clin J Am Soc Nephrol*** 2010; 5: 905-911.
20. Bucharles S, Barberato SH, Stinghen AE, Gruber B, Piekala L, Dambiski AC, et al. Impact of cholecalciferol treatment on biomarkers of inflammation and myocardial structure in hemodialysis patients without hyperparathyroidism. ***J Ren Nutr*** 2012; 22: 284-291.
21. Saab G, Young DO, Gincherman Y, Giles K, Norwood K, Coyne DW. Prevalence of vitamin D deficiency and safety and effectiveness of monthly ergocalciferol in hemodialysis patients. ***Nephron Clin Pract*** 2007; 105: 132-138.
22. Jean G, Terrat JC, Vanel T, Hurot JM, Lorriaux C, Mayor B, et al. Daily oral 25-hydroxycholecalciferol supplementation for vitamin D deficiency in haemodialysis patients: effects on mineral metabolism and bone markers. ***Nephrol Dial Transplant*** 2008; 23: 3670-3676.
23. Wang AY, Lam CW, Sanderson JE, Wang M, Chan IH, Lui SF, et al. Serum 25-hydroxyvitamin D status and cardiovascular outcomes in chronic peritoneal dialysis patients: a 3-y prospective cohort study. ***Am J Clin Nutr*** 2008; 87: 1631-1638.
24. Armas LA, Andukuri R, Barger-Lux J, Heaney RP, Lund R. 25-Hydroxyvitamin D response to cholecalciferol supplementation in hemodialysis. ***Clin J Am Soc Nephrol*** 2012; 7: 1428-1434.
25. Marckmann P, Agerskov H, Thineshkumar S, Bladbjerg EM, Sidelmann JJ, Jespersen J, et al. Randomized controlled trial of cholecalciferol supplementation in chronic kidney disease patients with hypovitaminosis D. ***Nephrol Dial Transplant*** 2012; 27: 3523-3531.
26. Mathieu C, Jafari M. Immunomodulation by 1,25-dihydroxyvitamin D3: Therapeutic implications in hemodialysis and renal transplantation. ***Clin Nephrol*** 2006; 66: 275-283.
27. London GM, Guérin AP, Verbeke FH, Pannier B, Boutouyrie P, Marchais SJ, et al. Mineral metabolism and arterial functions in end-stage renal disease: potential role of 25-hydroxyvitamin D deficiency. ***J Am Soc Nephrol*** 2007; 18: 613-620.
28. Cohen-Lahav M, Douvdevani A, Chaimovitz C, Shany S. The anti-inflammatory activity of 1,25-dihydroxyvitamin D3 in macrophages. ***J Steroid Biochem Mol Biol*** 2007; 103: 558-562.
29. Takahashi K, Horiuchi H, Ohta T, Komoriya K, Ohmori H, Kamimura T. 1 alpha, 25-dihydroxyvitamin D3 suppresses interleukin-1beta-induced interleukin-8 production in human whole blood: an involvement of erythrocytes in the inhibition. ***Immunopharmacol Immunotoxicol*** 2002; 24: 1-15.
30. Pecoits-Filho R, Barany P, Lindholm B, Heimburger O, Stenvinkel P. Interleukin-6 is an independent predictor of mortality in patients starting dialysis treatment. ***Nephrol Dial Transplant*** 2002; 17: 1684-1688.
31. Forman JP, Curhan GC,Taylor EN. Plasma 25-hydroxyvitamin D levels and risk of incident hypertension among young women. ***Hypertension*** 2008; 52: 828-832.
32. D'Marco L, García I, Vega C. [Uric acid, atherosclerosis and vascular calcifications in chronic kidney disease]. ***Invest Clin*** 2012; 53: 52-59.