Low Levels of 1.25-Dihydroxy Vitamin D is associated with All-cause Mortality in Prevalent Hemodialysis Patients

Düşük Serum 1,25-Dihidroksi Vitamin D Seviyesi Prevelan Hemodiyaliz Hastalarında Tüm Nedenli Mortalite Öngörücüsüdür

ABSTRACT

It has been suggested that vitamin D contributes not only to bone mineral metabolism but also to important other physiological processes. Vitamin D levels have been associated with increased mortality in predialysis and incident HD patients, but no data is available on the association between vitamin D levels and survival in prevalant hemodialysis (HD) patients.

Five hundred and forty five prevalent hemodialysis patients were recruited. Time averaged laboratory values throughout the two years and base line serum 25-OH vitamin D and 1.25-OH vitamin D levels were determined. All-cause mortality was prospectively evaluated after 2-year follow-up period. 25-OH vitamin D levels were significantly lower in females and in patients with diabetes. 1.25-OH_2 vitamin D level was significantly lower in diabetics. After two years of follow-up period, in crude analysis low serum 25-OH and 1.25 OH_2 vitamin D levels were associated with all cause mortality. In adjusted Cox-regression analysis, 1.25-OH_2 vitamin D level, but not 25-OH, was found as an independent predictor for all-cause mortality. Low 1.25-OH_2 vitamin D level was also found as an independent predictor for all-cause mortality in non-diabetic study group even after inclusion of time averaged vitamin Dtherapy dosage.

Serum 1.25-OH vitamin D level is associated with all cause mortality in prevalant hemodialysis patients.

KEY WORDS: Vitamin D, Mortality, Hemodialysis

ÖZ

Vitamin D, kemik mineral metabolizması dışında da bir çok önemli fizyolojik süreçte rol oynamaktadır. İnsidan hemodiyaliz ve prediyaliz dönem hastalarda vitamin D düzeyi ile mortalite ilişkisi gösterilmiştir. Ancak prevelan hemodiyaliz hastalarında serum vitamin D düzeyi ile mortalite ilişkisi hakkında çok az veri vardır.

Bu çalışmaya 545 prevelan hemodiyaliz hastası alındı. Hastaların bazal serum 25-Hidroksi ve 1,25-Dihidroksi vitamin D düzeyleri ve 2 yıl boyunca zamansal ortalamalı laboratuvar verileri belirlendi. Tüm nedenli mortalite, prospektif olarak bu 2 yıl sonunda incelendi. 25-Hidroksi vitamin D kadınlarda ve diyabetiklerde anlamlı olarak daha düşük saptandı. 1,25-Dihidroksi vitamin D de aynı şekilde diyabetiklerde anlamlı daha düşük saptandı. İki yıl sonunda, 25-Hidroksi ve 1,25-Dihidroksi vitamin D düzeyleri, prevelan hemoidiyaliz hastalarında tüm nedenli mortalite öngörücüsü olarak saptandı. Cox regresyon analizinde 1,25-Dihidroksi vitamin D düzeyi bağımsız tüm nedenli mortalite öngörücüsü olarak saptandı. Diyabetik olmayan prevelan hemodiyaliz hastalarında aktif vitamin D tedavisi modele eklendiğinde bile 1,25-Dihidroksi vitamin D düzeyi bağımsız tüm nedenli mortalite öngörücüsü idi.

Serum 1,25-Dihidroksi vitamin D düzeyi prevelan hemodiyaliz hastalarında tüm nedenli mortalite öngörücüsüdür.

ANAHTAR SÖZCÜKLER: Vitamin D, Mortalite, Hemodiyaliz

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INTRODUCTION

It has been suggested that vitamin D contributes not only to bone mineral metabolism but also to some physiological processes, such as hypertension, insulin resistance, inflammation, cell proliferation, immune system modulation and vascular calcification (1-6). Many studies in non uremic patients reported that vitamin D levels are associated with increased mortality (7-9). Although it has been shown that low vitamin D level is a predictor for early all cause mortality in incident HD patients (10), no data is available on the relationship between vitamin D levels and all-cause mortality in prevalant hemodialysis (HD) patients. The aim of this study was to prospectively investigate the impact of serum 25-OH and 1.25-OH_2 vitamin D levels on all-cause mortality in prevalent HD patients.

MATERIALS and METHODS

Subjects

Between December 2005 and March 2006, 545 of the 853 prevalent patients undergoing hemodialysis at eight Fresenius Medical Care Dialysis Units, who had serum available and met the inclusion and exclusion criteria were recruited in this prospective observational study. There was no difference regarding demographical, clinical and laboratory parameters between the patients recruited and not-recruited into the study. All-cause mortality was prospectively evaluated after 2-year follow-up period.

Inclusion criteria were to be aged between 18-80 years, being on at least 12 hours/week bicarbonate thrice weekly, chronic HD and willingness to participate in the study. Patients with serious life-limiting co-morbid situations such as active malignancy, infection, end-stage cardiac, pulmonary or hepatic disease, and those who were pregnant or lactating were excluded.

Patient characteristics was mean age of 58 ± 14 years (18-80), 46% female, HD duration 54 ± 45 months (24-336 months), and prevalence of diabetes 22%. Use of vitamin D was 14%, high flux membrane 30-60%, calcium-based phosphate (either calcium acetate or carbonate) binder 89%. No patient was on sevelamer or alluminum-containing phosphate binders. No patient was on sevelamer or alluminum-containing phosphate binders. The percentages of dialysates, containing 1.25, 1.50 and 1.75 mmol/L calcium were 6%, 38%, and 56%, respectively. Ultra-pure dialysate has been used in 10% of dialysis machines.

All patients gave signed informed consent. The study protocol was reviewed and approved by the local institutional ethics board. The study was conducted according to the principles of the Declaration of Helsinki.

Laboratory Measurements

Blood samples were drawn using uniform techniques after fasting immediately before the single mid-week dialysis session. Serum samples were then centrifuged within 2 hours and stored at -70°C until studied. Intact PTH was measured by using 2nd generation Roche Elecsys assay (Roche Diagnostics, Mannheim, Germany). All measurements were performed at a central laboratory, registered to several external quality services.

Serum 25-OH and 1,25-OH_2 vitamin D levels were measured by commercially available Radioimmunoassay (Biosource Europe S.A.-Rue de I'Industrie Nivelles-Belgium) at baseline. Intra and inter-assay CV were 4% and 5.2% in 25-OH vitamin D measurement; intra and inter-assay CV were 10.2% and 12.5% in 1.25-OH_2 vitamin D assay.

Statistical analysis

The association between vitamin D levels and other variables was assessed using Pearson's correlation analysis. All-cause mortality predictors were assessed by Cox regression analysis, cumulative survival by Kaplan-Meier analysis.

RESULTS

Baseline demographical, clinical and laboratory data of the study patients are listed in (Table I). The frequency of patients with spKt/V>1.2 was 88%, serum phosphate>5.5 mg/dl 14%, and iPTH<150 pg/ml 70%. The number of patients taking erythropoietin medication was 181 and mean weekly dose was 5370 Unit. Intravenous iron was used in136 patients and mean weekly dose was 90 mg. There was only 10 patients, 1.42% of population, who take renin angiotensin system inhibitors, either enzyme inhibitor or receptor blocker.

Mean 25-OH vitamin D level was 39±23 ng/ml; 42% of the patients had 25-OH<30 ng/ml (25-OD vit D deficiency). Only 4% of the patients had 25-OH vitamin D level<10 ng/ml (severe 25-0H vitamin D deficiency). 25-OH vitamin D levels were significantly lower in females in comparison to males (31.6 ± 20.2 vs 45.6±25.0 ng/ml,respectively, p<0.001) and in patients with diabetes (31.1±18.2 vs 41.5±24.9 ng/ml, respectively, p<0.001). The mean 1,25-OH vitamin D level was 19.2 ± 12.4 pg/ml. 1,25-OH_2 vitamin D level was significantly lower in diabetics (17.4±11.3 vs 19.8±12.6 pg/ml, p<0.05).

During the follow-up (22 ± 7 months), 76 patients died. Comparison of patients who remained alive and who died are presented in (Table II). Patients who died were older, had higher frequency of diabetes, higher systolic blood pressure, higher hs-CRP levels, lower serum albumin and hemoglobin levels. 25-OH (34 ± 0.7 vs 39 ± 24 ng/ml, p<0.05) and 1.25 OH_2 vitamin D levels (15.8 ± 8.8 vs 19.8 ± 12.8 pg/ml, p<0.01) were lower in the patients who died.

1.25-OH_2 vitamin D levels were positively correlated with iPTH (r: 0.151, p<0.01) and inversely correlated with age (r: -0.102, p<0.05). There was no correlation present with any of the other parameters shown in (Table II).

Table I: Baseline demographical data (Mean ± SEM).

Variables	Mean ± SEM
Age (year)	58.3±14.1
Gender (M, %)	46
DM (%)	22
CVD (%)	21
BMI	24.0±4.3
Time on dialysis (months)	53.8±45.15
AVF (%)	83
IDWG	2.2±0.9
spKt/V	1.4±0.2
URR (%)	75.5±6.7
SBP (mmHg)	124.9±15.7
DBP (mmHg)	75.0±9.08
Calcium (mg/dl)	9.3±0.8
Phosphorus (mg/dl)	4.2±1.1
Ca x P (mg^2/dl^2)	39.5±11.1
PTH (pg/ml)	146.1±188.3
Hemoglobin (g/dl)	11.2±1.5
Albumin (g/dl)	3.9±0.3
hsCRP (mg/dl)	1.5±2.9
Cholesterol (mg/dl)	180.6±45.5
Triglyceride (mg/dl)	162.0±101.1
HDL (mg/dl)	39.2±11.6
LDL (mg/dl)	109.2±35.9

CVD: history of cardiovascular disease; DM: Diabetes mellitus; BMI: body mass index; AVF: arteriovenous fistula; IDWG: interdialytic weight gain; spKT/V: single pool Kt/V; URR: urea reduction rate; SBP: systolic blood pressure; DBP: diastolic blood pressure; PP: pulse pressure; hsCRP: high sensitive C reactive protein; HDL:High density lipoprotein, LDL: Low density lipoprotein.

While 25-OH vitamin D levels were only slightly lower in the patients who died, 1.25-OH_2 vitamin D was lower. When the patients were grouped according to their 1.25-OH_2 vitamin D levels, cumulative survival was significantly higher in patients who had higher 1.25-OH_2 vitamin D levels (Figure 1). Correlations of serum 25-OH vitamin D levels with other parameters are listed in (Table III).

In adjusted Cox-regression analysis, 1.25-OH_2 vitamin D level, but not 25-OH, vitamin D was found as an independent predictor for all-cause mortality besides age, systolic blood pressure, serum albumin and hs-CRP level (Table IV).

Low 1.25-OH_2 vitamin D level was found as an independent predictor for all-cause mortality in non-diabetic study group (n=423) even after inclusion of time-averaged vitamin D therapy dosage into the model (Table V).

Table II: Comparison of patients who remained alive and who died.

	Alive patients n:469	Patiets who died n:76	P value
Age (year)	57±14	65±11	<0.001
Gender (F, %)	46	46	NS
Time on dialysis (months)	54±45	56±43	NS
DM (%)	20	34	0.008
CVD (%)	19	30	0.02
SBP (mmHg)	124±15	130±18	0.002
Calcium (mg/dl)	9.2±0.6	9.1±0.5	NS
Phosphate (mg/dl)	4.8±0.9	4.6±1.2	NS
PTH (pg/ml)	297±283	211±256	0.01
Total cholesterol (mg/dl)	165±39	157±42	NS
Triglyceride (mg/dl)	174±97	151±71	NS
Hs-CRP (mg/dl)	1.37±1.28	3.30±3.85	<0.001
25-OH vit D (ng/ml)	**39.9±24.3**	**34.4±0.7**	**0.04**
1.25 vit D (pg/ml)	**19.8±12.8**	**15.8±8.7**	**0.01**
Vit D dose (mcg/week)	**0.31±0,63**	**0.08±0.22**	**<0.001**
Phosphate binder dose (g/day)	**2.24±1,72**	**0.92±0.12**	**<0.001**

CVD: history of cardiovascular disease; DM: Diabetes mellitus; SBP: systolic blood pressure; DBP: diastolic blood pressure; hsCRP: high sensitive C reactive protein. Vitamin D therapy is reported as time averaged results.

Table III: Parameters correlated with 25-OH vit D levels.

Parameters	r	p value
Age (year)	-0.102	0.01
Albumin (g/dl)	0.143	<0.001
Hemoglobin (g/dl)	0.197	<0.0001
Total cholesterol (mg/dl)	0.139	0.001
Triglyceride (mg/dl)	0.97	0.02
High-density lipoprotein (mg/dl)	0.149	0.001
Phosphate (mg/dl)	0.97	0.004
Ca-P product (mg^2/dl^2)	0.113	0.009
Hs-CRP (mg/dl)	-0.103	0.01
Urea reduction rate (%)	-0.162	0.0001
1,25-OH vit D (pg/ml)	0.175	<0.001

DISCUSSION

Our results indicated that only low 1.25-OH_2 vitamin D levels were associated with all-cause mortality in prevalent HD patients and 25-OH vitamin D levels with nutritional parameters, gender and diabetes status.

Table IV: Predictors of all-cause mortality in the study population (n=545).

Independent variables	ExpB (95% CI)	p value
Unadjusted		
25-OH vitamin D (per 1 ng/ml)	0.99 (0.98-1.00)	0.1
1,25-OH_2 vitamin D (per 1 pg/ml)	0.97 (0.94-0.99)	0.01
Adjusted		
Age (per 1 year)	1.04 (1.02-1.06)	<0.0001
Systolic blood pressure (per 1 mmHg)	1.02 (1.01-1.03)	0.002
Albumin (per 1 gr/dl)	0.10 (0.04-0.28)	<0.0001
Hs-CRP (per 0.1 mg/dl)	1.22 (1.11-1.34)	<0.0001
1,25- OH_2 vitamin D (per 1 pg/ml)	**0.97 (0.94-0.99)**	**0.03**

Variables included in the model: age, gender, diabetes, HD duration, CVD history, SBP, levels of albumin, hemoglobin and Hs-CRP.

Table V: Mortality predictors of nondiabetic study population (n=423).

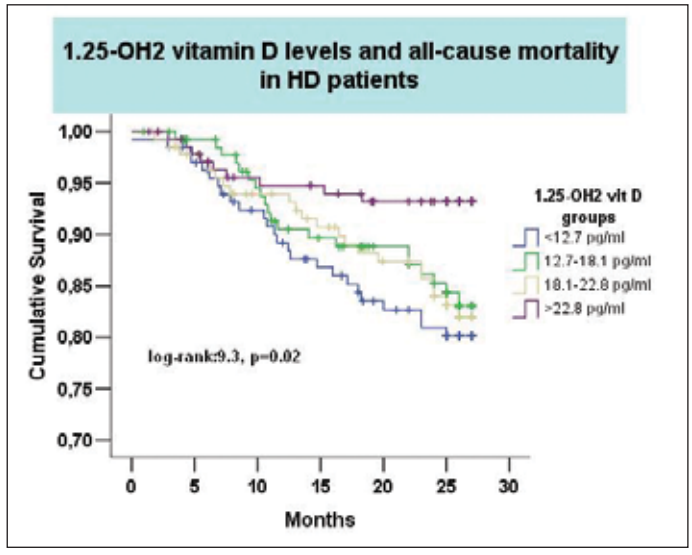
Independent variables	ExpB (95% CI)	p value
Adjusted		
Hs-CRP (0.1 mg/dl)	1.33 (1.19-1.49)	<0.001
Age (per 1 year)	1.03 (1.01-1.06)	0.01
Albumin (per 1 gr/dl)	0.19 (0.05-0.63)	0.007
1,25-OH_2 vitamin D (per 1 pg/ml)	**0.95 (0.92-0.99)**	**0.02**

Variables included in the model: age, gender, HD duration, CVD history, albumin, hemoglobin, Hs-CRP, SBP and time-averaged vit D dosage.

Patients with CKD are at high risk of vitamin D deficiency because of defective photoproduction of cholecalciferol due to uremic status (11). As the active form of vitamin D (1.25-dihydroxyvitamin D_3) is produced by the kidneys from 25-hydroxyvitamin D_3 (25-OH vitamin D, calcidiol), decrease of the former could be expected in these patients. However, contrary to this, reduced levels of both 25-OH and 1.25-OH_2 vitamin D had been reported in CKD as well as in HD patients (6,12-14).

Vitamin D plays a major role in calcium phosphorus metabolism; it is essential for bone homeostasis in healthy and chronic kidney disease (CKD) patients. Beyond the Ca-P-PTH axis, vitamin D is also important in many physiological

Figure 1: *Kaplan-Meier survival analysis of different 1,25-OH_2 vitamin D groups.*



systems (1-6). The role of bone and mineral abnormalities in cardiovascular disease of patients with CKD and the relationship between vitamin D levels and patient outcome has received increasing attention in past decades (15-18). In a three-year prospective cohort investigation in chronic peritoneal dialysis patients (19), low 25-OH vitamin D levels were shown to be a risk factor for cardiovascular events. In hemodialysis patients, one study reported that both 25-OH and 1.25-OH_2 vitamin D deficiencies were associated with increased early all-cause mortality during the first 90 days after start of dialysis treatment (10).

The presented study is the first study to prospectively investigate the relationship between vitamin D levels and all-cause mortality, as well as clinical parameters, in a 2-year follow-up in prevalent HD patients. We showed that only low 1.25-OH_2 vitamin D levels were associated with all-cause mortality in prevalent HD patients. In univariate analysis, 25-OH vitamin D level was also associated with all-cause mortality, whereas this was lost after adjusting for other nutritional markers. 25-OH vitamin D level was associated predominantly with nutritional parameters, gender and diabetes status as also reported by others (11). Although the direct causal relationship between 25-OH vitamin D and cardiovascular disease has not been established, geographic latitude, presumably due to the inadequate sun exposure and winter season are associated with increased cardiovascular disease in this group which 25-OH vitamin D levels are the lowest (20). The seasonal variations in 25-OH vitamin D levels may effect the study results in any cohort. In our study the long term follow up period removes one important distinction factor. The appropriate geographic latitude besides

the low diabetes rates in our study cohort, may explain the high levels of 25-OH vitamin D levels. If we consider that low levels of 25-OH vitamin D are also associated with well-established cardiovascular disease risk factors, such as hypertriglyceridemia, obesity and hypertension (21-23), and cardiovascular mortality in incident hemodialysis patients (10), our high 25-OH vitamin D levels may not be reflected in mortality.

Our results contradict to the study by Wang et al (19), who reported that low serum 25-OH vitamin D levels are associated with cardiovascular mortality in peritoneal dialysis patients. The authors found that very low levels of 25-OH vitamin D levels were associated with fatal cardiovascular events. However, in our study population, only 10% of the patients had 25-OH vitamin D levels<10 ng/mL. The difference in dialysis modality may have also yielded this difference. As we know peritoneal dialysis patients have more residual renal function as compared to HD patients.

In the study by Wolf M. et al (10), the authors reported that low vitamin D level is a predictor for all cause mortality (24%) in the first 90 day period in incident HD patients. These data are hard to apply to prevalent HD patients due to difference in mortality risks associated in the first 90 days (10). More recently Ravani et al showed that low serum 25-OH vitamin D levels predict kidney disease progression and death in patients with stage 2-5 CKD (24). The relatively older patients without HD and small sample size made difficult to compare their results with our patients' outcome. Finally, different sun exposure (25), and percentage of diabetes may explain these discrepancies.

The association between hypertension and vitamin D levels is not clear. Some reports showed lower vitamin D level associate with higher blood pressure (26) while some did not (27). We did not find significant correlations between both 25-OH and 1.25-OH_2 vitamin D levels and bood and pulse pressures. However it is important to point out that pathophysiology of blood pressure regulation in HD population is more complex and different from normal population.

Lower annual mortality rates in our study may probably be due to the strict volume control strategy apllied in our centers, as shown by mean SBP and DBP of patients. Previously, our group has shown that strict volume control is associated with better cardiac functions and less all cause mortality (28-33). Good control of hypertension observed in our population diminishes the effect of hypertension on mortality and the vascular system and therefore provides a clearer effect for the association reported in this paper. Any medication which can alter mortality rates in patients with end stage renal disease, such as statins, erythropoietin, intravenous iron and renin angiotensin system inhibitors were the same in study patients who were alive and those that were not.

In conclusion, low 1.25-OH_2 vitamin D levels are associated with higher all-cause mortality in prevalant hemodialysis patients.

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