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Low serum 25-OH vitamin D levels are associated with increased D/P creatinine ratio in peritoneal dialysis patients

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Abstract

Low 25-OH vitamin D levels have been linked to peritonitis and cardiovascular mortality in peritoneal dialysis (PD) patients. In this study we aimed to investigate the association of 25-OH vitamin D levels with peritoneal membrane characteristics in chronic PD patients. Consecutive 103 PD patients were enrolled in this retrospective study. Peritoneal dialysate to plasma (D/P) creatinine increase more than 0.1 with time were accepted as significant according Roc curve analysis. Patients with and without an increase in the D/P creatinine ratio of 0.1 were classified as Group 1 and Group 2, respectively. The relationship between baseline 25-OH vitamin D and peritoneal membrane characteristics were investigated. Mean age of the patients was 53.4±14.9 years and duration of PD was 72.1±50.3 months. There were thirty (29.1%) patients in Group 1. The duration of PD [73.5 (52.3-133.8) vs 49.0 (33.5-94.0) months, p:0.008]; hemoglobin [11.4 (10.4-12.2) vs. 10.2 (9.4-11.0) g/dL, p:0.001]and PTH [500.5 (254.5-748.3) vs 329.0 (205.0-549.5)ng/mL, p:0.047] levels were significantly higher in Group 1, whereas 25-OH vitamin D levels [5.0 (3.0-9.3) vs 7.8 (4.5-11.1)µg/L, p:0.027] and CRP [4.0 (3.0-7.2) vs. 8.0 (3.0-13.5)mg/L, p:0.028] were significantly lower. Multivariate analysis revealed duration of PD [Exp(B):1.012 (95%CI:1.001-1.022), p:0.028]; hemoglobin [Exp(B):1.756 (95%CI:1.199-2.571), p:0.004]; C-reactive protein (CRP) [Exp(B):0.882 (95%CI:0.789-0.985), p:0.026] and 25-OH vitamin D [Exp(B):0.853 (95%CI:0.754-0.965), p:0.012] were independent predictors of an increase in D/P creatinine ratio in PD patients. Increased D/P creatinine ratio was negatively correlated with 25-OH vitamin D level (r: -0.217, p:0.028). Lower levels of initial 25-OH vitamin D were associated with an increase in D/P creatinine ratio over-time.

Keywords: Inflammation, 25-OH vitamin D, chronic kidney disease, D/P creatinine ratio, peritoneal dialysis

Introduction

The 25-OH vitamin D deficiency is very common in chronic kidney disease and dialysis patients due to factors such as secondary hyperparathyroidism and hyperphosphatemia [1]. Loss of vitamin D in the dialysate effluent is an additional risk factor in PD patients [2]. Apart from its well-known effects on bone metabolism, vitamin D has pleiotropic effects associated with clinical outcomes such as all-cause mortality and peritonitis risk in PD patients [3]. However, the relation between vitamin D and peritoneal membrane characteristics is less clear.

Vitamin D has potent anti-inflammatory, anti-angiogenic and anti-fibrotic properties. It exerts its immune-modulatory effects by several mechanisms like inhibiting monocyte/macrophage pro-inflammatory cytokine production, modulating the expression of Toll-like receptors (TLRs) and the co-receptor CD14 [4-6]. Vitamin D reduces peritoneal fibrosis by activating regulator T cells, decreasing IL-17 production and inhibiting the epithelial-mesenchymal transition (EMT) in the peritoneal mesothelium. Several recent trials have even shown a protective role of vitamin D against peritoneal fibrosis [7-11].

In this study we aimed to investigate the association of 25-OH vitamin D levels with peritoneal membrane characteristics in chronic PD patients.

Materials and Methods

Study design

This is a single center, retrospective study including 103 incident PD patients followed at Marmara University peritoneal dialysis outpatient clinic. The study was approved by local ethics committee (Protocol code: 09.2020.1154). The investigation conforms with the principles outlined in the Declaration of Helsinki. All subjects gave informed consent of participation. One hundred seventy-two

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patients receiving peritoneal dialysis treatment with baseline 25-OH vitamin D were included in the study. The baseline and last peritoneal equilibration tests (PET) were used in analysis. Patients were excluded if they had malignancy or peritonitis, infectious or non-infectious inflammatory disease within the preceding 3 months, patients under the age of 18 years or those receiving 25-OH vitamin D or calcitriol supplementation at baseline. Baseline demographic characteristics, laboratory values and 25-OH vitamin D levels were recorded from patient charts. The peritoneal equilibration test was performed according to the method described by Twardowski in 1987 [12]. Dialysis adequacy was assessed with KT/V. The dialysis and residual components of KT/V were calculated based on 24-h urine and dialysate collections performed prior to the study entry. Residual renal function was expressed as the mean value of sum of the residual urea and creatinine clearances. Peritonitis episodes and peritoneal membrane characteristics at baseline and last visit were recorded. According to KDOQI guidelines levels <5 ng/mL of 25-OH vitamin D were considered severely deficient [13]. ROC curve analysis demonstrated that severe 25-OH vitamin D deficiency predicted 0.1 increase in D/P creatinine with 82.3 % specificity and 40.5% sensitivity (Area under curve: 0.507, CI:0.383-0.632). Accordingly, peritoneal D/P creatinine increase more than 0.1 with time were accepted as significant.

Statistical analysis

Statistical analysis was performed using he Statistical Package for the Social Sciences for Windows, version 22.0 (SPSS, Chicago, IL, USA). All variables that are distributed normally expressed as mean + std. deviation, and variables that are distributed non-normal expressed as median values and 25th-75th percentiles. To assess the influence of tested parameters on increased D/P creatinine ratio, Cox multivariate regression analysis is performed. Pearson's correlation is used to measure the degree of association between increased D/P creatinine ratio and 25-OH vitamin D. Statistical significance was set to $P<0.05$.

Results

There were 103 consecutive PD patients included in analysis. The mean age of the patients was 53.4±14.9 years and the duration of PD was 72.1±50.3 months. Mean serum 25-OH vitamin D levels were 8.2±5.3 µg/L. Seventy-eight patients (75.7 %) were on continuous ambulatory peritoneal dialysis (CAPD), while 25 patients (24.3%) were on automated peritoneal dialysis (APD). The causes of kidney disease were diabetes mellitus in 18 (17.5%) patients, hypertension in 27 (26.2%), glomerulonephritis in 30 (29.1%), vesico-ureteral reflux in 6 (5.8%), polycystic kidney disease in 7 (6.8%), nephrolithiasis in 3 (2.9%) and unknown in 12 (11.7%) patients.

Patients with and without an increase in D/P creatinine ratio of at least 0.1 during follow-up were classified as Group 1 and Group 2, respectively. Thirty (29.1%) patients showed an increase in peritoneal D/P creatinine over time and those patients had lower serum 25-OH vitamin D than Group 2 [5.0 (3.0-9.3) vs 7.8 (4.5-11.1) µg/L, p: 0.027]. The duration of PD [73.5 (52.3-133.8) vs 49.0 (33.5-94.0) months, p: 0.008], hemoglobin [11.4 (10.4-12.2) vs 10.2 (9.4-11.0) g/dL, p: 0.001] and PTH [500.5 (254.5-748.3) vs 329.0 (205.0-549.5) ng/mL, p: 0.047] levels were significantly higher in Group 1, whereas BUN [52.5 (41.3-65.0) vs 64.0 (49.5-79.0), mg/dL, p: 0.006] and CRP [4.0 (3.0-7.2) vs. 8.0 (3.0-13.5) mg/L, p: 0.028] were significantly lower. Number of peritonitis episodes [21 (70.0%) vs 47 (64.4%), p: 0.652] and glucose exposure [87.3 (54.4-188.4) vs 106.6 (65.9-147.4) mg/day, p: 0.593)] were similar between the two groups. Baseline demographic characteristics and laboratory data of the groups are shown in Table 1 and Table 2.

Table 1. The demographic and clinical characteristics of the groups

Variable	Group 1 (n:30)	Group 2 (n:73)	P value
Age, years	51.0 (40.5-63.3)	55.0 (43.5-64.0)	0.420
Sex, male, n (%)	17 (56.7%)	34 (46.6%)	0.354
Body mass index, kg/m^2	24.6 (21.4-28.1)	26.1 (23.1-29.9)	0.177
Duration of PD, months	73.5 (52.3-133.8)	49.0 (33.5-94.0)	0.008
Type of PD, CAPD, n (%)	22 (73.3%)	56 (76.7%)	0.718
Peritonitis, n (%)	21 (70.0%)	47 (64.4%)	0.652
Glucose exposure, mg/day	87.3 (54.4-188.4)	106.6 (65.9-147.4)	0.593
Causes of ESRD			
Diabetes mellitus, n (%)	5 (16.7%)	13 (17.8%)	0.890
Hypertension, n (%)	8 (26.7%)	19 (26.0%)	0.835
Nephritis, n (%)	9 (30.0%)	21 (28.8%)	0.648
Vesico-ureteral reflux, n (%)	1 (3.3%)	5 (6.8%)	0.491
Polycystic kidney, n (%)	0 (0%)	7 (9.6%)	0.080
Nephrolithiasis, n (%)	1 (3.3%)	2 (2.7%)	0.871
Unknown, n (%)	4 (13.3%)	8 (11.0%)	0.430

CAPD: Continuous ambulatory peritoneal dialysis; D/P: Dialysate/plasma; ESRD: End stage renal disease; PD: Peritoneal dialysis. Data presented as median (25th-75th percentiles).

Table 2. The laboratory parameters of the groups

Variable	Group 1 (n:30)	Group 2 (n:73)	P value
Glucose, mg/dL	93.5 (84.0-110.0)	91.0 (84.0-100.5)	0.416
Blood urea nitrogen, mg/dL	52.5 (41.3-65.0)	64.0 (49.5-79.0)	0.006
Creatinine, mg/dL	8.4 (6.6-9.7)	7.6(5.7-10.1)	0.296
Albumin, g/dL	3.8 (3.6-4.2)	3.7 (3.4-4.1)	0.109
Uric acid, mg/dL	5.8 (4.9-6.7)	6.1 (5.3-7.2)	0.157
Total cholesterol, mg/dL	197.0 (173.8-221.3)	194.0 (166.5-228.0)	0.905
Triglyceride, mg/dL	137.5 (118.5-193.3)	137.0 (103.5-187.0)	0.977
HDL cholesterol, mg/dL	42.0 (35.8-52.5)	45.0 (37.5-56.5)	0.525
LDL cholesterol, mg/dL	127.0 (101.5-140.5)	117.0 (89.0-145.5)	0.355
Aspartate transaminase, U/L	13.0 (10.8-15.0)	14.0 (10.0-18.0)	0.409
Alanine transaminase, U/L	12.0 (9.0-17.5)	13.0 (9.5-18.0)	0.483
Calcium, mg/dL	9.1 (8.6-9.6)	8.9 (8.3-9.4)	0.229
Phosphorus, mg/dL	4.8 (3.8-5.5)	5.0 (4.2-5.8)	0.284
Sodium, mEq/L	137.0 (135.0-139.3)	137.0 (135.0-140.0)	0.651
Potassium , mEq/L	4.8 (4.1-5.4)	4.4 (3.8-5)	0.073
Parathyroid hormone, ng/L	500.5 (254.5-748.3)	329.0 (205.0-549.5)	0.047
25-OH vitamin D, µg/L	5.0 (3.0-9.3)	7.8 (4.5-11.1)	0.027
Ferritin, µg/L	264.0 (137.5-448.3)	257.0 (154.5-479.0)	0.870
HbA1C, %	5.5 (4.7-5.9)	5.3 (5.0-5.7)	0.802
Leukocyte, *10^3/ µL	7.5 (6.5-9.3)	7.4 (6.0-8.9)	0.687
Hemoglobin, g/dL	11.4 (10.4-12.2)	10.2 (9.4-11.0)	0.001
Platelet, *10^3/ µL	248.0 (200.5-306.3)	264.0 (180.5-310.5)	0.948
C-reactive protein, mg/L	4.0 (3.0-7.2)	8.0 (3.0-13.5)	0.028

D/P: Dialysate/plasma; eGFR: estimated glomerular filtration rate; HDL: High density lipoprotein; LDL: Low density lipoprotein; Data presented as median (25th-75th percentiles)

Baseline D/P creatinine ratio [0.59 (0.56-0.63) vs 0.74 (0.66-0.81), p: <0.001] was significantly lower in Group 1, whereas final D/P creatinine ratio [0.75 (0.69-0.84) vs 0.68 (0.62-0.75), p: <0.001] was significantly higher. Peritoneal permeability characteristics were significantly different among the groups. Baseline and final PET results of the study groups are summarized in Table 3.

Table 3. Peritoneal equilibrium test measurements of the groups in the first and last visit

	Baseline			Last		
	Group 1 (n:30)	**Group 2 (n:73)**	**P value**	**Group 1 (n:30)**	**Group 2 (n:73)**	**P value**
Dialysate volume, mL	8000.0 (6000.0-8000.0)	7000.0 (6000.0-8000.0)	0.316	8000.0 (6000.0-10.000.0)	8000.0 (6000.0-9950.0)	0.571
Ultrafiltration, mL	900.0 (500.0-1010.0)	746.0 (500.0-867.5)	0.078	665.0 (500.0-881.6)	750.0 (500.0-875.0)	0.325
Urine volume, mL	625.0 (37.5-1612.5)	900.0 (50.0-1400.0)	0.809	75.0 (0.0-800.0)	350.0 (0.0-1162.5)	0.206
eGFR, ml/min/1.73 m^2	2.4 (0.1-6.1)	3.3 (0.1-6.9)	0.586	0.2 (0.0-2.9)	0.9 (0.0-3.5)	0.398
nPCR, g/kg/day	0.9 (0.8-1.0)	1.0 (0.8-1.1)	0.504	0.9 (0.8-1.4)	0.9 (0.8-1.2)	0.687
KT/V	2.1 (1.8-2.5)	2.1 (1.7-2.4)	0.509	2.0 (1.8-2.3)	1.9 (1.6-2.3)	0.270
D/P creatinine	0.59 (0.56-0.63)	0.74 (0.66-0.81)	<0.001	0.75 (0.69-0.84)	0.68 (0.62-0.75)	<0.001
PET permeability, n (%)			<0.001			<0.001
High	1 (3.3%)	22 (30.1%)		11 (36.7%)	9 (12.3%)	
High average	5 (16.7%)	38 (52.1%)		17 (56.7%)	42 (57.5%)	
Low	1 (3.3%)	3 (4.1%)		0 (0.0%)	5 (6.8%)	
Low average	23 (76.7%)	10- (3.7%)		2 (6.7%)	17 (23.3%)	

D/P: Dialysate/plasma; eGFR: Estimated glomerular filtration rate; nPCR: Normalized protein catabolic rate; PET: Peritoneal equilibrium test; UF: Ultrafiltration. Data presented as median (25th-75th percentiles)

Multivariate analysis showed that the duration of PD [Exp (B) (95% CI): 1.012 (1.001-1.022), p: 0.028]; hemoglobin [Exp (B) (95% CI): 1.756 (1.199-2.571), p: 0.004]; CRP [Exp (B) (95% CI): 0.882 (0.789-0.985), p: 0.026] and 25-OH vitamin D [Exp (B) (95% CI): 0.853 (0.754-0.965), p: 0.012] were independent predictors of increased D/P creatinine ratio in PD patients (Table 4).

Table 4. Independent predictors of increased D/P creatinine in the multivariate analysis

Variables	Exp (B)	95% CI	P value
Duration of Peritoneal Dialysis, months	1.012	1.001-1.022	0.028
Haemoglobin, g/dL	1.756	1.199-2.571	0.004
C-reactive protein, mg/L	0.882	0.789-0.985	0.026
25-OH vitamin D, µg/L	0.853	0.754-0.965	0.012
Parathyroid hormone, ng/L	1.001	0.999-1.003	0.291

The Pearson correlation test revealed that increased D/P creatinine ratio was negatively correlated with 25-OH vitamin D (r: -0.217, p:0.028) and CRP levels (r: -0.215, p:0.029) and was positively correlated with duration of PD (r: 0.291, p:0.003) and parathyroid hormone levels (r: 0.220, p:0.026).

Discussion

In the present study we showed that lower vitamin D levels were associated with an increase in D/P creatinine ratio over time in peritoneal dialysis patients. Vitamin D deficiency is common among dialysis patients and PD patients have an even higher risk to develop deficiency of vitamin D as 25-OH vitamin D is lost during dialysis via the peritoneal effluent [14,15]. Long-term peritoneal dialysis causes chronic inflammation and morphological changes in the peritoneal membrane resulting in functional loss, technique failure and premature discontinuation of PD therapy [9]. Apart from its well-known effects on bone metabolism, vitamin D prevent inflammation and fibrosis. Vitamin D exerts anti-inflammatory effects by inhibiting monocyte/macrophage pro-inflammatory cytokine production and expression of toll-like receptor 2 (TLR-2) [4,5]. Another factor leading to a change in peritoneal membrane structure is the epithelial to mesenchymal transition (EMT) of mesothelial cells [16,17].

Some studies have also demonstrated protective effects of vitamin D on peritoneal fibrosis. Lee et al showed that calcitriol protects against peritoneal fibrosis by decreasing transforming growth factor-β1 and angiotensin II production [11]. Liu et al demonstrated that the expression of EMT-associated biomarkers was inhibited by calcitriol in an in-vitro cell model of peritoneal fibrosis [18]. In another study, oral paricalcitol reduced tissue remodelling during chronic experimental PD, preventing loss of ultrafiltration capacity and technical failure [19]. In our study we demonstrated that PD patients with lower vitamin D levels had an increase in D/P creatinine ratio over time. Our findings support the hypothesis that vitamin D exerts protective effects against peritoneal fibrosis, possibly through the mechanisms mentioned above.

Longer PD durations are associated with chronical inflammation due to uremia, loss of RRF, peritonitis episodes and exposure to dialysis solutions [10]. Peritoneal inflammation may also cause an increase in D/P creatinine ratio over time and has been associated with high peritoneal membrane permeability [11,14]. In our study, even though patients with an increase in D/P creatinine ratio had a longer PD duration, their CRP level was lower, which is in contrast with current literature. There may be several explanations for our findings. First, this was a cross-sectional study with a single CRP measurement whereas there may be marked variation in CRP levels reported in individual patients over time for no obvious reasons [20]. Secondly, systemic and local intraperitoneal inflammation represent distinct underlying processes and thus are not always correlated [21].

Peritonitis promotes changes in peritoneal transport functions and negatively affects the long-term survival of both peritoneal membrane and patients [22]. Several recent studies have shown a possible relationship between vitamin D levels and peritonitis. In a study by Pi et al, 25-OH vitamin D levels could predict peritonitis in 346 PD patients [23]. Other studies showed that treatment with oral vitamin D was associated with a decreased risk of peritonitis [24,25]. However, we were unable to show a correlation between vitamin D levels and peritonitis rates.

The present study has several limitations. It is a retrospective, cross-sectional study with a relatively small number of patients. Since it is an observational study, it is not possible to determine a cause-effect relationship. Furthermore, markers of peritoneal inflammation were not measured.

In conclusion, low 25-OH vitamin D was associated with an increase in D/P creatinine ratio over time. Further studies with larger number of patients are needed to investigate the impact of vitamin D on functional and structural changes of the peritoneal membrane.

Conflict of interests
The authors declare that they have no competing interests.

Financial Disclosure
All authors declare no financial support.

Ethical approval
The study was approved by the Ethics committee of Marmara University medical school (Protocol code: 09.2020.1154)

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