BANTAO Journal 2011; 9 (1): 23-25

BJ
BANTAO Journal

Original article

The Relationship Between Vitamin D Levels, Proteinuria and Blood Pressure in Patients with Chronic Kidney Disease

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Abstract

Introduction. Proteinuria and hypertension are the risk factors for progression of chronic kidney disease. The aim of this study is to investigate whether there is a relationship between vitamin D and proteinuria as well as blood pressure in patients with chronic kidney disease.
Methods. Forty patients (20 male, 20 female) were enrolled on this study. In patients, 24 h urine protein excretion, and biochemical tests including 1, $25(OH)_2D_3$ and $25(OH)D_3$ blood levels were obtained. Data analysis was performed using SPSS, windows version 15.0. A p value of less than 0.05 was considered statistically significant.
Results. Data analysis showed no relationship between $1,25(OH)_2D_3$ levels and proteinuria as well as systolic or diastolic blood pressure (p=0.90, p=0.56, p=0.64 respectively). Also $25(OH)D_3$ levels were not found to be statistically relevant to proteinuria (r=-0.273, p=0.09). Furthermore, no relationship was found between $25(OH)D_3$ levels and either systolic or diastolic blood pressure (p=0.06, p=0.79 respectively).
Conclusion. Further prospective studies with larger patient samples are needed to determine whether there is a relationship between vitamin D and proteinuria as well as blood pressure.

Key words: blood pressure, chronic kidney disease, proteinuria, vitamin D

Introduction

Chronic kidney disease (CKD) is an important problem of the public health. Proteinuria is both an important finding in patients with CKD and a factor affecting the progression of CKD [1].
Apart from its classical role in serum calcium and phosphorus metabolism, vitamin D has additional important effects. $1,25(OH)_2D_3$ stimulates the differentiation of various cell types and decreases cell proliferation. It has been shown that $1,25(OH)_2D_3$ prevents interstitial fibrosis by decreasing Transforming Growth Factor–beta (TGF-β) and by increasing the formation of Hepatocyte Growth Factor (HGF) [2]. It has been suggested that low vitamin D levels are related to an increase in blood pressure [3,4]. In the literature, the data suggesting a relationship between vitamin D, proteinuria and blood pressure in humans is extremely rare. The purpose of this study was to examine whether there is a relationship between vitamin D levels and proteinuria as well as blood pressure (BP) in patients with CKD or not.

Material and methods

This study was carried out on forty patients (20 males and 20 females) with CKD stage 3-4 for at least three months. The exclusion criteria were accepted as the following; CKD stage 5, use of vitamin D or phosphorus binding drugs, diabetes mellitus, congestive heart failure, and malignancy.
Patients who met the inclusion criteria were informed of the study and signed an informed consent. The study was approved by the Ethical Committee of Medical Faculty of Kocaeli University.

Laboratory

All biochemical and urine tests were performed at the Biochemistry Laboratory of Kocaeli University Medical Faculty. Patients were informed on 24-hour urine collection. The blood samples were taken after a period of 8-12 hours of fasting, in a sitting position.
Biochemical and urine samples were analyzed on an Abbott /Aeroset system device (TM) following the manufacturer's recommendations. Parathyroid hormone (PTH) levels were measured by using immunohistochemical method on Immunlite 2000 Analyser. Urinary protein excretion was measured with turbidimetric method. Creatinine clearance was calculated according to the following formula:
Creatinine clearance: UC x UV / SC x 1440
(UC=Urinary creatinine level (mg/dl), UV=Urine volume (ml/d), SC=Serum creatinine level (mg/dl), 1440=Value of the 24-hour period in minutes).

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To measure vitamin D level, blood samples were immediately centrifuged and then serum was kept at -80 °C up to the time of analysis. $1,25(OH)_2D_3$ levels were assessed with radioimmunoassay method on a ISO-DATA BIOS device. The reference range for $1,25(OH)_2D_3$ was determined as 15.9-55.6 pg/ml. $25(OH)D_3$ level were measured by the method of high performance liquid chromatography (HPLC) on the Thermo-Spectra System device. The reference range was determined as 25-100 mmol/1.

BP was measured by a cuff-type sphygmomanometer device. After at least 10 minutes in the sitting position, the mean of three measurements obtained from the right arm at 10 minute intervals was calculated. Korotkoff's first sound was recorded as systolic BP and Korotkoff's fifth sound was recorded as diastolic BP.

Statistical Analysis

Data is presented as mean ± standard deviation. The statistical analyses were performed with the SPSS 15.0 Windows version. Pearson correlation test was used to analyze the relationships between the variables. A p value of less than 0.05 was considered statistically significant.

Results

Table 1. Baseline characteristics of patients

Parameter	Mean ± SD
Age (years)	47.25±13.41
Body mass index (kg/m^2)	25.57±4.50
$1,25(OH)_2D_3$ (pg/ml)	10.71±8.30
$25(OH)D_3$ (mmol/l)	22.91±18.47
Proteinuria (mg/day)	1486.18±1700.73, median: 926.03
Albumin (gr/dl)	4.31±0.44
Creatinine clearence (ml/min)	26.61±8.56
Creatinine (mg/dl)	3.09±1.66
Parathyroid hormone (pg/ml)	262.50±159.44
Calcium (mg/dl)	9.01±0.69
Phosphorus (mg/dl)	4.02±1.08
Glucose (mg/dl)	94.60±8.72
Systolic blood pressure (mmHg)	145.25±18.94
Diastolic blood pressure (mmHg)	89.50±8.45

The baseline characteristics of the study population are presented in the Table 1. The etiology of CKD was hypertension in 26 patients, polycystic kidney disease in 6, chronic glomerulonephritis in 3, amyloidosis in 2, vesicourethral reflux in 1, preeclampsia in 1and nephrolithiasis in 1patient.

Twenty-five patients (62%) were receiving treatment with renin angiotensin system (RAS) blockers. Angiotensin converting enzyme (ACE) inhibitors were given in 13 patients, angiotensin (AT) II type 1 receptor blockers (ARBs) in 11 patients and both ACE inhibitor and ARB was given in 1 patient. Fifteen patients (38%) were not on any ACE inhibitor or ARB. $1,25(OH)_2D_3$ level was low in 32 patients (78%) and within normal limits in eight patients (%22). $25(OH)D_3$ level was low in 25 patients (62%) and within the normal limits in I5 patients (38%).

Table 2. The association between $1,25(OH)_2D_3$ and proteinuria, and blood pressure

Parameter	P
Proteinuria (mg/day)	0.90
Systolic blood pressure (mmHg)	0.56
Diastolic blood pressure (mmHg)	0.64

No significant relationship was found between $1,25(OH)_2D_3$ levels and proteinuria, or BP. Additionally, $25(OH)D_3$ levels were not significantly correlated with proteinuria, or diastolic BP. Interestingly, a marginally significant correlation was observed between $25(OH)D_3$ and systolic BP (p=0.06). The results are summarized in Tables 2 and 3.

Table 3. The association between $25(OH)D_3$ and proteinuria, and blood pressure

Parameter	P
Proteinuria (mg/day)	0. 09
Systolic blood pressure (mmHg)	0.06
Diastolic blood pressure (mmHg)	0.79

Discussion

In our study, we found that neither $1,25(OH)_2D_3$, nor $25(OH)D_3$ levels were significantly related to the degree of proteinuria. Although the RAS inhibitors are used to decrease proteinuria [5], neither the ACE inhibitors nor the ARBs are able to prevent CKD or to reduce proteinuria to normal levels. It is suggested that vitamin D may affect urinary protein excretion by several mechanisms.

In subtotally nephrectomized rats, it was found that the combination of enalapril and paricalcitol decreased protein excretion, machrophage infiltration and formation of monocyte chemoatractant protein-1 (MCP-1) mRNA whereas increased TGF- β mRNA expression more than enalapril alone [6]. In another study, 22-oksacalcitriol and calcitriol were shown to decrease glomerulosclerosis and albuminuria, mesangial cell proliferation and formation of glomerular TGF- β [7]. It was also shown that $1,25(OH)_2D_3$ reduced proteinuria, glomerular volume, neutrophil and monocyte accumulation as well as production of interleukin-6 [8]. 22-oksacalcitriol has been shown to decrease albuminuria, glomeruler volume, cellularity and sclerosis [9].

In patients with CKD stage 3-4, the administration of paricalcitol for 24 weeks was found to decrease proteinuria in 31% of 94 patients. This decrease was determined to be 3.3 times that of the control group. Furthermore, proteinuria decreased in 52% of paricalcitol treated patients who also received ACE inhibitor or ARBs. This ratio remained as 27% in the control group [10]. Another study reported that the prevalence of albuminuria in patients with low $25(OH)D_3$ levels was higher than that in patients with normal $25(OH)D_3$ levels ($P<0.001$) [11]. In a prospective study carried out on 10 patients with IgA nephropathy, the effect

of calcitrol on proteinuria, kidney function, TGF-β and ATII levels was examined for a period of 12 weeks. A significant decrease of proteinuria (p=0.03) was observed with calcitrol. It was also shown a decrease of TGF-β levels decreased and this decrease was significantly related to the decrease of proteinuria (P=0.02) [12].

The antiproteinuric effect of vitamin D has been mainly examined in rat models. Unfortunately, most of the studies performed in humans were not prospective, and included a small series of patients. Moreover, measurement methods were sometimes semiquantitative.

In some studies, it is suggested that there is a relationship between the vitamin D levels and BP and/or plasma renin activity. Renin and ATII production were shown to increase in the experimental subjects without vitamin D receptor. It was found that plasma renin level was increased in animals with a low $1,25(OH)_2D_3$ synthesis and that $1,25(OH)_2D_3$ suppressed renin transcription and then its plasma level. It was also shown that a decrease in vitamin D levels is related to the increase of BP [3,4]. On the other hand, another study showed that calcitriol did not decrease ATII level and BP [12].

In this study, $1,25(OH)_2D_3$ and $25(OH)D_3$ levels were not related to systolic and diastolic BP. These results may be attributed to the limitations of the study, such as the small sample size and the cross-sectional design of the study.

In conclusion, vitamin D levels were not significantly associated with proteinuria and BP in our analysis. Prospective randomized controlled studies are needed to evaluate the relationship between vitamin D levels, proteinuria and BP.

Conflict of interest statement. None declared.

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