Pleiotrophic Effects of Vitamin D in Proteinuric Chronic Kidney Disease Patients

Proteinürisi Olan Kronik Böbrek Hastalarında Vitamin D'nin Pleotrofik Etkileri

ABSTRACT

OBJECTIVE: Proteinuria is an important marker that accelerates chronic kidney disease. Known anti-proteinuric treatments are not always sufficient. In recent years, animal studies have shown that vitamin D has positive effects on inflammation in the kidney, glomerulosclerosis, interstitial fibrosis. The aim of our study was to investigate the effect of vitamin D on proteinuria in patients with proteinuric chronic kidney disease (CKD).

MATERIAL and METHODS: Thirty-five patients with proteinuric chronic kidney disease (CKDp) were included in the study [Study Group(SG)]. Vitamin D3 (300000 u / 21 d for 3 months) was added to therapy without any drugs modifications. Thirty-nine patients was consisted CKDp (CG). None of the patients had used vitamin D and/or phosphorus-binding medication in the previous 6 months. The results of daily proteinuria and biochemical tests at the beginning of study and the end of 3 months were recorded.

RESULTS: In the SG, there was significant improvement in proteinuria (median 1813 mg to 1395 mg p = 0.03), serum total protein and albumin (p=0.04 and p=0.02 respectively) at the end of 3 months. The BUN and creatinine values did not change. There was no significant difference in any parameter in CG. The percentage of patients with reduced proteinuria according to baseline was higher in SG (74%) when compared to CG (43%) (p=0.007).

CONCLUSION: In CKDp patients, vitamin D for 3 months significantly decreased proteinuria without causing a deterioration in renal function or an adverse event. Vitamin D may therefore be an alternative option to anti-proteinuric treatment in proteinuric CKD patients, in addition to its other known effects.

KEY WORDS: Chronic kidney disease, Proteinuria, Vitamin-D

ÖZ

AMAÇ: Proteinüri kronik böbrek hastalığını hızlandıran önemli bir belirteçtir. Proteinüriyi azaltmada bilinen anti-proteinürik tedaviler her zaman yeterli olmamaktadır. Son yıllarda hayvan deneylerinde vitamin D'nin böbrekteki inflamasyon, glomerüskleroz, interstisyel fibroz üzerine olumlu etkileri gösterildi. Çalışmamızın amacı proteinürik kronik böbrek hastalarında vitamin D'nin proteinüri üzerine etkisini araştırmaktır.

GEREÇ ve YÖNTEMLER: Çalışmaya 35 proteinürik kronik böbrek hastası (KBH) alındı [Çalışma grubu (ÇG)]. ÇG'unda tedaviye hiçbir değişiklik yapılmadan 3 aylık vitamin D3 (300000 u/21gün) eklendi. Otuzdokuz proteinürik KBH kontrol grup (KG)'unu oluşturdu. Tüm hastalar son 6 ayda vitamin D ve/veya fosfor bağlayıcı ilaç kullanmıyordu. Hastaların başlangıç ve 3. ay sonundaki günlük proteinüri ve biyokimyasal test sonuçları kaydedildi.

BULGULAR: Çalışma grubunda üç ayın sonunda proteinüride anlamlı azalma (medyan 1813mg dan 1395mg p=0.03), serum total protein ve albumin düzeyinde anlamlı artma saptandı (p=0.04 ve p=0.02 sırası ile). BUN ve kreatinin değerleri değişmedi. KG'unda tüm parametrelerde anlamlı farklılık saptanmadı. Başlangıca göre proteinürisi azalan hasta yüzdesi, KG'una göre (%43) ÇG'unda (%74) daha fazla idi (p<0.007). Olumsuz etki gözlenmedi.

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SONUÇ: Proteinürik KBH'larında 3 aylık Vitamin D tedavisi ile böbrek fonksiyonlarında bozulma olmadan proteinüride önemli azalma, albüminde artış saptadık. Sonuç olarak bilinen etkilerinin yanında Vitamin D, proteinürik KBH'larında alternatif anti-proteinürik bir tedavi seçeneği olabilir.

ANAHTAR SÖZCÜKLER: Kronik böbrek hastalığı, Proteinüri, Vitamin-D

INTRODUCTION

Proteinuria is a risk factor for the development of end-stage renal disease in both the general population and in chronic kidney disease (CKD) patients (1).

Under optimal conditions, each renin-angiotensin-aldosterone system (RAAS) blocking agent is able to reduce proteinuria by around 40% (2). Addition of another RAAS blocking agent results in only 25% further reduction of proteinuria.

Vitamin D can reduce residual proteinuria through both RAAS-dependent and RAAS-independent pathways (3). In a cross-sectional study, a high prevalence of calcidiol deficiency was found in CKD patients (4). Although the definite critical serum 25(OH) vitamin D level and benefits of 25(OH) vitamin D supplement in CKD patients remain controversial, the 2009-KDOQI guideline suggested that patients with serum 25(OH) vitamin D < 30 ng/ml should receive supplementation with nutritional vitamin D (5).

Vitamin D acts primarily on the calcium-phosphate homeostasis and bone metabolism. However, studies have demonstrated that vitamin D receptor and 1α hydroxylase activity are present in many tissues and organ structures. Vitamin D is considered to have autocrine and paracrine effect in tissues and organs. In recent studies, it has been shown that vitamin D has a favorable effect on immunity, vascular functions, cardiomyocyte health, inflammation, insulin resistance and renal functions (6). Active vitamin D has been demonstrated to both lessen RAAS and intraglomerular pressure and reduce fibrosis, apoptosis and inflammation in animal models (7). These effects might improve renal injury. We therefore investigated the effect of vitamin D therapy on proteinuria and renal function in patients with proteinuric CKD in this study.

PATIENTS and METHODS

Thirty-five patients with proteinuric chronic kidney disease (CKDp) were included in the study [study Group (SG)]. Thirty-nine CKDp patients not using vitamin D made up the control group (CG). None of the patients had used vitamin D and/or phosphorus-binding medication in the last 6 months. The results of daily proteinuria and biochemical tests at the beginning of the study and the end of 3 months were recorded.

All patients had proteinuria, chronic kidney disease (CKD) and well controlled blood pressure, with no changes in drug treatment for the last 6 months. Active infection, heart failure, malignant disease, acute renal injury, history of surgery, liver disease, malabsorption, treatment with phosphate binders and vitamin D therapy (including calcitriol, paricalcitriol) were exclusion criteria.

SG patients were treated with orally administered an ampoule containing 300.000IU vitamin D3 every three weeks without changing their treatment for 3 months. We preferred the ampoule of cholecalciferol because it was cheaper than D vitamin analogues and the ability to receive it at once instead of daily drops, preventing patients from skipping a dose. Blood urea nitrogen (BUN), creatinine, total protein, albumin, calcium, phosphorus, and daily proteinuria were measured at month 0 and 3 in all patients. Based on the glomerular filtration rate (GFR) calculated according to the MDRD formula, SG were divided into 3 groups: GFR>60 ml/min (G1), 30-60 ml/min (G2), and 15-30 ml/min (G3). Furthermore, patients in the SG were divided into subgroups based on patients with/without diabetes mellitus (DM), and with/without angiotensin converting enzyme inhibitor/angiotensin receptor (ACEI/ARB) use to compare all the parameters.

STATISTICAL ANALYSIS

The SPSS 15.0 packet program was used for analysis of data. The frequency and percentage distribution of data is provided. As a result of the normality test, the Independent Samples t Test was used for normally distributed variables in pairwise groups to evaluate differences between the groups, and the Mann-Whitney U test was used for non-normally distributed variables. The Kruskal-Wallis H Test with Bonferroni correction was used for non-normally distributed variables in non-pairwise groups. To evaluate differences between the groups, the significance level considered was 0.05.

RESULTS

There were no differences in age, gender and primary kidney disease between the groups.

The primary kidney diseases of patients were due to DM, glomerulonephritis, amyloidosis and unknown cause. Table I shows the comparison of some biochemical parameters of the SG and CG at month 0 and 3. In SG, there was significant improvement in proteinuria (median 1813 mg to 1395 mg p=0.03), serum albumin (p=0.02) and total protein (p=0.04) (Table I). GFR, BUN and creatinine values did not change. There was no significant difference in any parameters in CG. The percentage of patients with reduced proteinuria according to baseline was higher in SG (74%) when compared to CG (43%)

(p <0.007) (Table II). Figure 1 shows the changes in proteinuria at third month according to baseline in SG and CG. Also in SG, serum albumin levels were significantly increased in non-diabetic patients and in patients who did not take ACEI/ARB (Table III,IV) and proteinuria was significantly reduced in SG especially when GFR was lower than 30 ml/min (Table V). In SG, the calcium level remained the same but the phosphorus level was significantly increased, although within acceptable limits.

Table I: Comparison of some biochemical parameters of study group (SG) and control groups (CG) at month 0 and 3.

	SG (35) mean±std	**p**	**CG (39) mean±std**	**p**
BUN0 mg/dL	29.29±16.99	0.32	27.13±17.86	0.91
BUN3 mg/dL	30.89±19.21		26.97±18.050	
Creatinine0 mg/dL	1.91±1.25	0.71	1.68±1.20	0.32
Creatinine3 mg/dL	1.93±1.36		1.72±1.20	
Total protein0 g/dL	6.54±0.62	**0.04**	6.75±0.70	0.21
Total protein3 g/dL	6.70±0.83		6.66±0.72	
Albumin0 g/dL	3.60±0.51	**0.02**	3.66±0.55	0.74
Albumin3 g/dL	3.74±0.54		3.64±0.57	
Calcium0 mg/dL	9.10±0.42	0.32	9.12±0.42	0.22
Calcium3 mg/dL	9.18±0.57		9.19±0.38	
Phophorus0 mg/dL	3.73±0.72	0.14	3.62±0.70	0.96
Phosphorus3mg/dL	3.92±0.66		3.62±0.68	
Proteinuria0 mg/day Median*	2627.51±2547.65 1813,00	***0.03**	2145,95±2408,21 1068,00	*0.44
Proteinuria3 mg/day Median*	2256.71±2194,31 1395.00		2213.62±2425.38 1278.00	

p values of mean±SD and median **(*)** values.

Table II: Changes in proteinuria at end of 3. month according to baseline in study and control group.

Protenuria	SG (35)	CG (39)	**p**
Increase	25.7% (n=9)	56.4% (n=22)	**0.007**
Decrease	74.3% (n=26)	43.6% (n=17)	

Table III: In study group patients with/without diabetes mellitus, comparison for daily proteinuria and biochemical parameters of baseline and third month.

Parameters	**Study Group**					
	DM Group (n=11)			**Non-DM Group (n=24)**		
	0 Months	**3 Months**	**p**	**0 Months**	**3 Months**	**p**
Total protein g/dL	6.67±0.6	6.94±1	NS	6.49±0.62	6.60±0.72	NS
Albumin g/dL	3.35±0.47	3.45±0.56	NS	3.71±0.51	3.88±0.48	**0.042**
Calcium mg/dL	9.05±0.49	8.86±0.87	NS	9.13±0.38	9.29±0.39	NS
Phosphorus mg/dL	3.95±0.79	3.87±0.61	NS	3.65±0.72	3.95±0.70	**0.021**
Proteinuria mg/dL median*	2893±3535 (1092)	2768±3526 (735)	*0.155	2489±1949 (1904)	2067±1470 (1774)	*0.081

p values of mean±SD and median **(*)** values (related samples wilcoxon signed rank test), **NS:** Non significant.

Table IV: Comparison of parameters in study group (SG) patients with/without ACE/ARB at month 0 and 3.

Parameters	Study Group					
	Treated with ACE-I/ARB (n=24)			Non-treated with ACE-I/ARB (n=11)		
	0 Months	3 Months	p	0 Months	3 Months	p
Total protein g/dL	6.37 ±0.59	6.42±0.70	NS	6.94±0.45	7.35±0.71	**0.021**
Albumin g/dL	3.52±0.52	3.63±0.54	NS	3.75±0.51	4±0.45	**0.036**
Calcium mg/dL	9.09±0.43	9.20±0.52	NS	9.14±0.39	9.05±0.77	NS
Phosphorus mg/dL	3.73±0.78	3.95±0.74	NS	3.77±0.71	3.87±0.48	NS
Proteinuria mg/day	2973±2686 (1965)	2554±2374 (1774)	NS *0,063	1837±1947 (1092)	1707±2066 (663)	NS *0,248

p values of mean±SD and median **(*)** values (related samples wilcoxon signed rank test)

Table V: Comparison of parameters in study group divided according to GFR at month baseline and at the end od third month.

Parameters	Study Group								
	SG1 (GFR>60 ml/min n=15)			SG2 (GFR 30-60 ml/min n=9)			SG3 (GFR (15-30 ml/min n=11)		
	0 Months	3 Months	p	0 Months	3 Months	p	0 Months	3 Months	p
Total protein g/dL	6.39±0.53 (6.40)	6.40±0.61 (6.30)	NS	6.63±0.82 (6.90)	6.81±1 (7.20)	NS	6.69±0.51 (6.70)	7.05±0.83 (7.10)	NS
Albumin g/dL	3.65±0.51 (3.70)	3.72±0.51 (3.60)	NS	3.66±0.49 (3.70)	3.82±0.55 (3.90)	NS	3.46±0.51 (3.80)	3.73±0.61 (3.90)	0,036
Calcium mg/dL	9.30±0.37 (9.30)	9.43±0.31 (9.50)	NS	9.01±0.38 (8.80)	9.08±0.63 9.00()	NS	8.92±0.4 (9.00)	8.85±0.75 (9.10)	NS
Phosphorus mg/dL	3.44±0.63 (3.50)	3.63±0.53 (3.60)	NS	3.37±0.42 (3.20)	3.76±0.25 (3.80)	0,028 *0,012	4.5±0.6 (4.5)	4.3±0.77 (4.30)	NS
Proteinuria mg/day	2590±1740 (1970)	2427±2437 (1395)	NS *0,281	1553±2033 (714)	1423±1418 (1036)	NS *0,809	3630±3414 (2596)	2805±2617 (2450)	0,026

p values of mean±SD and median **(*)** values (related samples Wilcoxon signed rank test)

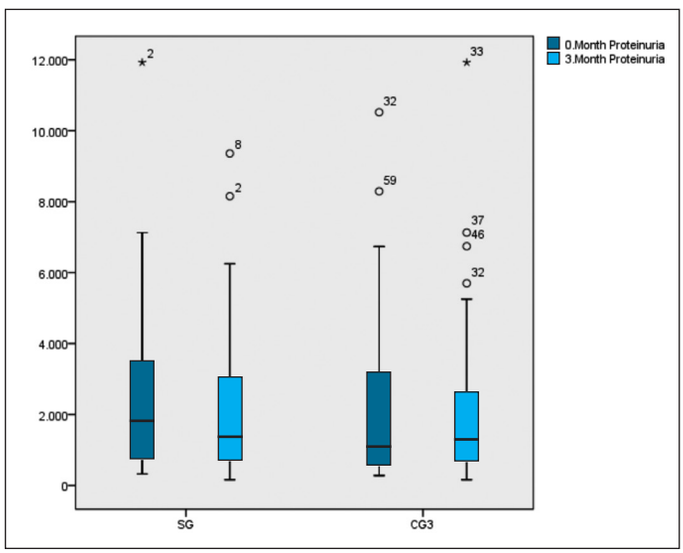

Figure 1: *Changes in proteinuria at third month according to baseline in study and control group*

DISCUSSION

Many experimental and clinical studies have demonstrated the role of proteinuria in the progressive loss of renal functions. Conservative measures to reduce proteinuria such as salt restriction, prevention of becoming overweight, well controlled blood pressure and blood glucose, and the use of renin-angiotensin-aldosterone system inhibitors are inadequate to completely prevent progression of kidney disease. Therefore, new strategies are needed. Vitamin D has been shown to have autocrine and paracrine effect on many tissues and organs in addition to calcium-phosphorus and bone metabolism.

Vitamin D deficiency is highly prevalent in patients with CKD even in the early stage (8). In several studies, vitamin D deficiency has been related to albuminuria, lower glomerular filtration rate and CKD progression (9-11). The guidelines on the management of CKD-related bone and mineral disorders suggest that hypovitaminosis D should be corrected (5). Our study was intended to observe whether vitamin D had anti-proteinuric effect

and renal functions. Studies supplementing with the equivalent of 700-1000 IU/day suggested that daily doses of vitamin D >2000 IU could be required to achieve optimal vitamin D status. High doses like 50000 IU/week or 300000/ month were employed in some studies and they reported that high dose oral cholecalciferol can be used safely and effective for correcting vitamin D deficiency in CKD (12,13). In our study, 300.000 IU Vitamin D3 was orally administered every three weeks without changing the primary treatment of our proteinuric patients. We determined that proteinuria significantly decreased in SG at the end of 3 months. Compared to CG, proteinuria significantly decreased in SG. The number of patients with decreased proteinuria compared to the baseline was statistically higher in SG than CG. Similar to our study, there are other studies that have detected an association of vitamin D deficiency with albuminuria and GFR in patients with CKD. However, vitamin D analogues such as calcitriol and paricalcitriol were used in these studies. We used cholecalciferol in our study because there are studies suggesting that cholecalciferol increases the calcitriol level in CKD and acts on the parathormone level (14,15). How vitamin D provides an anti-proteinuric effect is described in experimental studies. Analogues of vitamin D delivered to rats undergoing subtotal nephrectomy have been shown to regress hypertrophy and glomerulosclerosis compared to those that did not receive vitamin D (16). This effect appeared to occur by blocking the release of renin in the renin angiotensin aldosteron system (17-19). Experimental studies has also suggested that vitamin D not only protects the glomerular structure but also tubular structures, prevents transformation of tubule epithelium into mesenchymal epithelium, and has an anti-fibrotic effect by inhibiting transformation of interstitial fibroblasts into myofibroblasts (20).

Renal functions (BUN, creatinine) did not statistically significantly change with vitamin D therapy for 3 months in SG as in CG in our study. There are confounding studies related to the effects of vitamin D on GFR. GFR was found to be reduced in the VITAL study, but the GFR did not change in our study and the study by Liu et al. (21,22).

In SG patients with/without DM, and treated with/without ACEI/ARB, the proteinuria levels were decreased compared to the baseline but they were not significant. However in SG, the serum albumin levels were significantly increased in nondiabetic patients and patients not treated with ACEI/ARB. The most prominent anti-proteinuric effect of vitamin D was found in SG patients with proteinuric stage IV CKD. The serum albumin level also significantly increased in the same group. It can be said that a Vitamin D effect could be detected more easily in advanced stage kidney failure. Among our patients, adverse events such as hypercalcemia or hyperphosphatemia did not develop. The serum phosphate level increased within acceptable limits.

The limitations of our study include the limited number of patients, the short time of treatment, and the lack of analysis of serum levels of vitamin D and parathormone.

In conclusion, proteinuria was significantly reduced without adverse effects in patients treated with vitamin D. Also vitamin D caused improvement of serum albumin and total protein levels in proteinuric chronic kidney disease. In conclusion, vitamin D may be an alternative nonspecific anti-proteinuric treatment option in proteinuric chronic kidney disease patients.

COMPLIANCE WITH ETHICAL STANDARDS

Conflict of interest: All authors declare that they have no conflict of interest.

Ethical approval: The protocol of the study was conducted in accordance of the ethical principles stated in the declaration of Helsinki. This study has been approved at the ethics committee of the Medical Faculty of Çukurova University, at meeting number 16 on February 14. 2013

Informed consent: Informed consent was obtained from all individual participants included in the study.

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