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MANUSCRIPT TITLE: INFLUENCE OF ACTIVE VITAMIN D THERAPY ON PROTEINURIA AND GLOMERULAR FILTRATION RATE IN PATIENTS OPERATED ON KIDNEY TRANSPLANTATION.

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ABSTRACT

Background: Vitamin D deficiency is frequently seen in the studies performed on kidney transplantation patients. This study, aimed at comparing the influences of active vitamin D therapy on the proteinuria and glomerular filtration rate (GFR) in kidney transplant patients. **Methods:** The patients were divided into two groups: patients having parathormone (PTH) level >400 pg/ml, no diabetes and kidney transplantation and patients with PTH level < 400 pg/ml. The first group received 25 µg of active vitamin D /day. Vitamin D, complete blood count, biochemical parameters and used immunosuppressive drug levels (steroid, tacrolimus) were recorded for all patients. The patients underwent the active vitamin D therapy for six months, once in every 15 days. Vitamin D was serologically studied through the HPLC **(**high-performance liquid chromatography) method. **Results:** The proteinuria level baseline values of the patients getting the active vitamin D therapy were 158.09±58.84 mg/day in the 0^{th} month and 123.32±51.74 mg/day in the 6^{th} month (p: 0.02). These values were 124±22 mg/day and 122±23.1 mg/day in the control group, respectively. The baseline values of GFR levels for the patients getting vitamin D therapy were 67.59±26.13 ml/min/1.73m^2 in the 0^{th} month, 76.45±14.23 ml/min/1.73m^2 in the 6^{th} month, and the p-value was 0.000 when it was considered in terms of the glomerular filtration rate. These values were 95±14 and 96±12.2 in the control group, respectively. While vitamin D baseline values were 8.6±6.2 ng/ml when it was evaluated in terms of vitamin D levels, vitamin D was found as 19.14±7.02 ng/ml in the 6th-month control (p: 0.0000). These values were 23.03±8.98 ng/ml and 21.02±6.78 ng/ml in the control group, respectively. While a negative correlation was determined between vitamin D level in the patients getting the active vitamin D therapy and proteinuria ($p<0.001$), a significant positive correlation was detected between the GFR levels ($p<0.001$). **Conclusions:** Vitamin D deficiency is highly seen in the patients who underwent kidney transplantation. There were no differences found between the patients who received and who did not receive the active vitamin D, in terms of age, body mass index (BMI), blood pressure, laboratory values (creatinine, lipid levels, haemoglobin, urea, uric acid) and donor features. Vitamin D plays a primary role in bone metabolism, Ca and P balance. Vitamin D provides regulatory influences in the renal, cardiac protection and immune system besides the metabolic functions in the kidney transplant patients, as a conclusion, Vitamin D level should be routinely checked in these patients in the light of these results.

KEYWORDS: Glomerula filtration rate, proteinuria, vitamin D, kidney transplantation.

INTRODUCTION

The chronic kidney disease (CKD) is a condition characterized by the chronic, progressive and irreversible nephron loss developing depending on the various diseases. These patients have applied for peritoneum dialysis, hemodialysis, and kidney transplantation as a renal replacement therapy at the present time. The kidney transplantation is the choicest therapy method of end-stage renal failure (ESRF) at present. It is a superior therapy compared to kidney transplantation methods since patient rehabilitation is at the top level and it has positive influences on the lifetime. Moreover, all kidney functions are recovered by kidney transplantation.[1, 2]

The most frequent mortality and morbidity causes are cardiovascular diseases in patients with ESRF. In addition to the classic risk factors in the patients with ESRF, the existence of uraemic toxins and risk factors such as chronic volume load, anaemia, chronic inflammation, calcium-phosphor balance disorders, and

nutrition disorders should be added to the clinical picture.[3]

Vitamin D is a steroidal hormone. Vitamin D, which was synthesized by the skin through the ultraviolet B (UV-B) lights or taken through a diet, transforms to vitamin D3, a biologic active form 1.25 $(OH)_2$ with the alpha hydroxylation as 25 in the liver and as 1 in the kidney, respectively. 1.25 $(OH)_2$ vitamin D3 levels specifically decrease in transplanted patients, compared to the healthy population, with the contribution of hyperphosphatemia together with the progressive nephron loss in chronic kidney failure. Previous studies have shown that vitamin D deficiency was more frequently seen in the people waiting for the kidney transplantation, vitamin D deficiency incidence was 30% and the insufficiency was 50% for the people who underwent kidney transplantation.[4] The declineof kidney function lead to vitamin D deficiency by gradually causing a decrease of 1.25 $(OH)_2$ vitamin D3 serum levels.

Vitamin D deficiency, depending on the less common nutrition disorder, is highly seen in the patients having kidney failure. The serum 1.25 $(OH)_2$ vitamin D levels start decreasing in the CKD phase 2 and vitamin D deficiency is frequently seen in all the phases of CKD including the ESRF.

It was proved that the existence of proteinuria might accompany the increasing loss of vitamin D metabolites together with a high loss of the protein binding vitamin D from the urine. Vitamin D receptor agonists were also shown in the animal models since they decreased the expression of the inflammatory mediators activated by the monocytes and T cells,providing the survival of the podocytes by preventing the differentiation and apoptosis induction and decreasing the albuminuria and glomerulosclerosis.[5,6,7]

We aimed at searching whether the active vitamin D therapy had a positive influence on the proteinuria and GFR in the kidney transplant patients compared to the control group. In the case where the positive results are obtained as a result of the study, vitamin D replacement will become a current issue to add without targeting the parathormone level, to increase the lifetime of the kidney in terms of its positive influences.

MATERIAL AND METHOD

Study Type

This is a prospective, randomized, controlled clinical study. The study was approved by University Ethical Committee of Clinical Investigations with the decision number (no:01.10.2013/335) dated December 2012.

Study Population

The study population consists of 124 patients (52 females, 72 males), who applied to the Renal Transplantation Polyclinic of the Department of Nephrology within the Faculty of Medicine, University of Gaziantep between December 2012 and May 2013, and whose regular controls were included in the study. The patients constituting the study group were admitted into the present study after being evaluated for the inclusion and exclusion criteria. The age, gender, and body mass index (BMI) data for both groups were matched. Fourty healthy people (20 females, 20 males) constituted the control group.

Subject Selection

The patients, who signed the informed consent form, older than 18 years old, constituting the study group, underwent kidney transplantation 3 months before. Their calculated GFR was > 30 ml/min 1.73 m^2 and serum creatinine was < 2mg/dL. They had a stable kidney function (the patients who did not show 2-fold or more increase in the serum creatinine in the last 3 months), and were included in the study. There were patients excluded from the study: cases with diabetes mellitus history, active urinary system infection, use of active vitamin D and returned to the dialysis, presence of neoplasm, an uncontrolled thyroid disease, a severe liver failure on the kidney transplantation more than one, myocardial infarct in the last 6 months or a acute rejection attack in the last 3 months.

Research Protocol

The parameters such as age, gender, body mass index and systolic-diastolic blood pressure used during the evaluation and follow-up were recorded. The biochemical parameters (blood urea nitrogen, creatinine clearance calculated by the MDRD (Modification of Diet in Renal Diseases), uric acid HDL-cholesterol, LDL-cholesterol, triglyceride levels and vitamin D levels were analyzed. Vitamin D, complete blood count, biochemical parameters and used immunosuppressive drug levels were recorded. Vitamin D was serologically studied through the HPLC (High-Performance Liquid Chromatography) method. The glomerular filtration rate measurement was calculated by the MDRD formula (eGFR = 175 x [(serum creatinine x 0.0113) -1.154] x (age-0.203) x 0.742 (only in females)). The active vitamin D 25µg/day was given to those whose PTH level was >400 pg/ml since they had no diabetes and underwent kidney transplantation, and to those whose PTH level was <400 pg/ml. The patients were divided into two groups for follow-up.

The proteinuria, calcium, phosphorus, parathormone, GFR, vitamin D level, uric acid and CRP parameters were analyzed before starting the active vitamin D therapy and after 6 months. Vitamin D was serologically studied through the HPLC **(**High-Performance Liquid Chromatography) method. The glomerular filtration rate measurement was calculated through the MDRD formula (eGFR = 175 x [(serum creatinine x 0.0113) -1.154] x (age-0.203) x 0.742 (only in females)).

The active vitamin D therapy (0.25-µg/day) was started first for the patients whose parathormone level was above 400-pg/ml the patients who underwent kidney transplantation.

Statistical methods

All the data was calculated as the mean ± standard deviation. The statistical analyses were made using the "Statistical Package for Social Sciences for Windows Version 15.0" (SPSS Inc.; Chicago, IL, USA) packaged program. The relationships between the variables were examined by the Pearson correlation test. The relationship between vitamin D levels with the serum creatinine and PTH levels was evaluated by the linear regression analysis. P <0.05 was considered significant.

RESULTS

There were not any significant differences of demographical and clinical data between the study and control group. The demographical and clinical data of all the participants are summarized in Table 1.

Table I: The demographical and clinical characteristics of the study and control group.

	Receiving active vitamin D therapy (n=64) (Group 1A)	Not receiving active vitamin D therapy (n=60) (Group 1B)	The p-value	Control group (n=40)	The p-value
Gender (M/F)	37/27	35/25	0.687	20/20	0.450
Age (year±SD)	36.44±11.18	37.09±11.45	0.711	41.64±16.50	0.841
BMI (kg/m^2±SD)	26.6 ± 2.9	25.0 ± 4.6	0.554	24.6 ±3.1	0.578
Time passed after the transplantation (month±SD)	16±6	17±5	0.167	-	-
Chronic GN (%)	22	17	0.789	-	-
HT (%)	20	19	0.867	-	-
Others(%)	22	24	0.643	-	-
HD/PD/Pre-empitivity (%)	45/3/2	40/2/4	0.344	-	-
Donor; Alive or relatives/cadaver	42/8	40/6	0.945	-	-
Steroid dose (mg/day±SD)	5.9 ± 2.7	5.4 ± 2.1	0.178	-	-
Tacrolimus dose (mg/kg/day±SD)	0.09±0.03	0.08±0.02	0.654	-	-
MAP (mmHg±SD)	118.6± 2.2	112.6 ± 1.6	0.08	112 ± 1.2	0.09

BMI: Body mass index, GN: Glomerulonephritis, HT: Hypertension, HD: Hemodialysis, PD: Peritoneum Dialysis, MAP: Mean Arterial Pressure

** p<0.001, *p<0.05

There wasn't any significant relationships between the GFR levels in patients receiving the active vitamin D therapy (Group 1A) (p=0.634) and the patients who didn't receive (Group 1B) this treament, and the GFR level was significantly highest in the control group (p<0.001). The parathormone and CRP levels were significantly higher in the group 1A compared to the group 1B (p<0.01). These variables were significantly low in the kidney transplant patients in comparison to the control group (p<0.01). There were no differences between the urea and uric acid levels in the groups 1A/1B, but they were statistically significantly lower in the control group (p<0.01) (Table 2).

Table II: The baseline laboratory parameters of the study group and the control group.

	Group 1A (n=64)	Group 1B (n=60)	The p-value	Control (n=40)	The p-value
Serum creatine (mg/dl)	1.21±0.33	1.31±0.49	0.765	0.94±0.32	0.125
GFR (ml/min)	67.59±26.13	72.13±17.73	0.634	95±14	0.001*
Serum albumin (g/dl)	5.03±1.4	4.53±0.63	0.876	3.95±0.51	0.965
Total cholesterol(mg/dl)	186 ± 34	175 ± 27	0.543	165±33	0.876
LDL-cholesterol (mg/dl)	104 ± 23	112±19	0.245	102±26	0.654
Triglyceride (mg/dl)	156 ± 77	148±56	0.248	146±64	0.324
Hemoglobin (g/dl)	12.7 ± 2.20	13.6 ± 2.3	0.854	12.4±1.55	0.765
Proteinuira(mg/day)	158.09±58.84	146.74±28.53	0.632	124±22	0.659
Calcium (mg/dl)	9.28±0.76	9.33±0.74	0.887	9.03±0.77	0.743
Phosphorus (g/dl)	4.1±0.91	4.5±0.70	0.780	2.87±0.73	0.654
PTH (pg/ml)	409.66± 334.50	225.21± 114.66	0.001**	68.79±14.45	0.000**
Urea (mg/dl)	52.33±10.53	49.58±11.49	0.543	28.82±9.85	0.002*
Vitamin D level (ng/ml)	8.6±6.2	10.4±7.5	0.08	23.03±8.98	0.0001**

Uric acid (mg/dl)	5.92±1.31	5.83±1.01	0.567	3.56±0.99	0.04*
CRP (mg/l)	12.45±6.53	9.36±5.87	0.004**	3.5±2.3	0.000**

GFR; Glomerular Filtration Rate, PTH; Parathormone, CRP;C-Reactive Protein
** p<0.001, *p<0.05

While there weren't any statistically significant differences of vitamin D levels in the groups 1A/1B active vitamin D therapy (p=0.08), vitamin D levels were significantly higher in the healthy control group (p<0.01) (Table 2).

Table III: The laboratory parameters in the 6th month for the patients Group 1A and 1B.

	Group 1A (n=64)	Group 1B (n=60)	The p-value
Proteinuira (mg/day)	123.56±21.16	142.76±18.97	0.003**
Calcium (mg/dl)	9.64±0.86	9.34±0.78	0.576
Phosphorus (g/dl)	2.1±0.86	3.4±0.12	0.03*
PTH (pg/ml)	157.35±130.37	131.06±93.831	0.458
GFR (ml/min)	76.14±12.23	74.11±13.64	0.764
Vitamin D level (ng/ml)	19.14±7.02	11.4±7.5	0.000**
Uric acid (mg/dl)	5.15±1.06	5.6±1.02	0.765
CRP (mg/l)	8.64±4.56	8.32±5.76	0.986

PTH; Parathormone, GFR; Glomerular Filtration Rate, CRP; C-Reactive Protein
** p<0.001, *p<0.05

There are significant differences related to proteinuria, phosphorus and vitamin D levels among both of groups. An explicit decrease was found in the parathormone levels, even though it was not significant (p: 0.458). A significant decrease was statistically seen in the proteinuria levels of the group 1A, in comparison to the proteinuria levels of our patients receiving and not receiving the active vitamin D therapy in the 6th month (p=0.003). The phosphorus level was significant lower in the group 1A compared to the group 1B (p=0.03). Vitamin D level was statistically higher in the group 1A in comparison to Group 1B (p<0.001).

The 0th-month and 6th-month comparisons of the group 1A and group 1B were showed in Table 4.

Table IV: Comparison between the Group 1A and 1B – before the treatment and after 6 months.

	Kidney Transplant Patients					
	Group 1A (n=64)		The p-value	Group 1B (n=60)		The p-value
	0th month	6th month		0th month	6th month	
Proteinuira (mg/day)	158.09±58.84	123.32±51.74	0.02*	146.74±28.53	142.56±38.54	0.763
Calcium (mg/dl)	9.28±0.76	9.64±0.86	0.323	9.33±0.74	9.34±0.78	0.377
Phosphorus (g/dl)	4.1±0.91	2.1±0.86	0.002*	4.5±0.70	3.4±0.12	0.08
PTH (pg/ml)	409.66±334.50	157.35±130.37	0.000**	225.21±114.66	131.06±93.831	0.000**
GFR (ml/min)	67.59±26.13	76.45±14.23	0.000**	72.13±17.73	74.60±14.54	0.09
Vitamin D level (ng/ml)	8.6±6.2	19.14±7.02	0.000**	10.4±7.5	11.4±7.5	0.213
Uric acid (mg/dl)	5.92±1.31	5.15±1.06	0.311	5.83±1.01	5.6±1.02	0.543
CRP (mg/l)	12.45±6.53	8.64±4.56	0.04*	9.36±5.87	8.32±5.76	0.112

PTH; Parathormone, GFR; Glomerular Filtration Rate, CRP; C-Reactive Protein
** p<0.001
*p<0.05

Statistically, the proteinuria, phosphorus, PTH and CRP level significantly decreased ingroup 1A in the 6th month, with p value 0,02 respectively. There were not any statistically significant differences of proteinuria, phosphorus and CRP levels before the treatment and in the 6th-month for the group 1B, with p value. 0.763 respectively.

It was noticed that the GFR and vitamin D level of the group 1A was statistically significantly increased in 6 months after receiving active vitamin D therapy compared to those group 1B. (p< 0.001).

After the therapy, a negative correlation was determined between vitamin D and proteinuria levels (p<0.001, correlation coefficient= -0.486), and a significant positive correlation was determined between vitamin D level and GFR level (p<0.001, correlation coefficient=0.583) in the group 1A.

DISCUSSION

Our study was prospectively performed on 124 kidney transplant patients being regularly followed-up and a healthy 40-person control group whose age, gender and BMI matched.

The active vitamin D therapy (0.25-µg/day) was administrated to the transplanted patients whose parathormone value was above 400-pg/ml. The patients whose parathormone value was under this level did not receive treatment. The patients' parameters before starting the active vitamin D therapy and in the 6th month after starting the therapy were compared. The parameters compared were proteinuria, calcium, phosphorus, parathormone, GFR, Vitamin D level, uric acid, and CRP. A relationship was determined for our patients in the significant level related to the proteinuria phosphor and vitamin D levels (the p-values were 0.02, 0.002, 0.000; respectively); an explicit decrease was determined in the parathormone levels even they were not statistically significant in their comparisons to the group 1A/1B for the parathormone levels (the p-value; 0.458). There weren't any significant differences when these parameters were compared in the group 1A/1B in terms of the calcium, GFR, uric acid and CRP ($p>0.05$).

A significant relationship was found between vitamin D and proteinuria in the patients whose parathormone level was high and who received the active vitamin D therapy. If vitamin D level increases, the proteinuria decreases. In the examinations performed backward for a study in which the influences of the paricalcitol on PTH were evaluated in the patients who were in the phase 3-4 CKD and whose secondary hyperparathyroidism were determined it was found that the proteinuria decreased by 31%; we had 94 patients receiving paricalcitol for 24 weeks; the proteinuria levels didn't change in 50% of them, increased in 19% of the cases and decreased in 15% of the patients. The control group had 101 patients; the proteinuria levels didn't change in 62% of them and increased in 23% of the cases. The decrease of proteinuria was of 3.2 - fold more in comparison to the control group receiving paricalcitol.[8] Lomonte et al showd that there was an inverse relationship between the serum 25 OH vitamin D level and proteinuria in 75 kidney transplant recipients.[9] The reasons of the negative relationship between the proteinuria and vitamin D are being prevented by the RAAS (Renin Angiotensin Aldosterone System) activation with vitamin D blockading the renin transcription and being hemodynamically decreased of the proteinuria and being prevented of this situation in vitamin D deficiency. It is argued that the detractive influence of the proteinuria by vitamin D might occur depending on the direct influences of it on the insulin resistance, cell proliferation, differentiation and apoptosis.[10]

A relationship was found between vitamin D and GFR in the patients whose parathormone level was high and who were receiving active D therapy. Accordingly, if vitamin D level increases, the GFR level also increases. There are studies which showed that vitamin D protects the graft functions.[11] The creatinine value decreased in the group receiving vitamin D for 3-year in the study performed by Uyar et al in Turkey.[12] In our study, there weren't any statistically significant differences before the treatment and in the 6th-month of the patients receiving and not receiving 6th-month active vitamin D therapy, but there was a significant difference between the GFR levels.

In our study, a significant relationship was determined in the positive relationship between the CRP and vitamin D. The various studies revealed that there was a relationship between vitamin D and inflammation, even the underlying mechanism could not be completely revealed in the patients with CKD. This study showed that the monocyte chemoattractant protein-1 (MCP-1) level and macrophage infiltration in urine were in an inverse relationship with the serum 1.25(OH)2D3 level, where a 10-unit increase of serum vitamin D levels was associated with the decrease of kidney inflammation.[13] It was revealed in the obstructive nephropathy models of the animal studies that the paricalcitol use decreased the inflammatory cell accumulation in the kidneys and RANTES (Regulated on Activation, Normal T Cell Expressed and Secreted) formation by preventing the nuclear factor kappa-beta influences through the VDR (Venereal Disease Search) in the kidneys.[14] The elevated CRP level was associated with the mortality depending on all the total and cardiovascular diseases.[15,16] In our study, the CRP value was high at the beginning and decreased after getting the active vitamin D therapy.

CONCLUSION

In conclusion, the recent studies show the influences of vitamin D on mineral metabolism have a wide spectrum. The evidence supporting this condition is the existence of the clinical and observational studies showing that the non-traditional vitamin D influences continue in a wide range in the immune, cardiovascular and kidney systems. The studies performed by the VDR signal agonists in recent years show that vitamin D supplements decrease the albuminuria. The observational studies performed in the small-scale show that there is a correlation between the low vitamin D level and a decrease in the GFR. In our randomized and controlled study, we found vitamin D levels were low independently from the PTH level. We got the positive influences on the proteinuria GFR and inflammation in the patients to whom we administrated vitamin D. We were faced with the paradigm of necessity to make vitamin D supplement due to its non-classic influences for each patient who underwent kidney transplantation.

However, there were some limitations to the study we performed. Our sample size is too small to generalize the data obtained. But, we believe that our study is important

in terms of encouraging the randomized and controlled extensive studies.

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NOTES

Authors' contribution

Irem AKIN ŞEN**:** Conceptualization, designanalysis, methodology, software, writing- reviewing and editing.
Özlem Tiryaki: Conceptualization, designanalysis, methodology, software, writing- reviewing and editing.
Cem ŞEN: Conceptualization , data curation, analysis, design, writing- original draft preparation, editing.

All authors read and approved the final version of the manuscript

Declarations of interest

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript

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