original article

The relationship between vitamin D levels and 24-hour ambulatory blood pressure in renal transplantation patients

Böbrek nakli hastalarında vitamin D düzeyi ile 24 saatlik ambulatuvar kan basıncı ilişkisi

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Geliş Tarihi: 30.07.2018 Kabul Tarihi: 06.08.2019 Doi: 10.21601/ortadogutipdergisi.449335

Abstract

Aim: GRenal transplantation is the most prominent treatment of renal insufficiency. Vitamin D deficiency found to be common in renal transplant patients. Through renin-angiotensin-aldosterone system inhibition, it protects from hypertension and cardiovascular diseases. In this study, we investigated the relation between vitamin D levels and 24-hour ambulatory blood pressure monitoring and parameters (body mass index, fasting plasma glucose, lipid profile) that may affect graft function.

Material and Method: Association of clinical parameters with vitamin D levels and blood pressure were prospectively compared in renal transplant patients. All patients blood pressure levels were evaluated by 24-hour ambulatory blood pressure monitoring.

Results: A total of 115 renal transplant recipients were enrolled in the study. Mean level of vitamin D was 16.28±5.2ng/ml, 10.4 % of the patients had severe vitamin D insufficiency (<10ng/ml), 70.4 % with a level between 10-20ng/ml. The vitamin D deficiency (10-20ng/ml) was seen more frequently in women than man. Patients has been divided into two groups, the first with levels of less than 20 ng/ml, the second one with levels of equal or higher than 20 ng/ml. There were no statistically significant difference in age, body mass index and donor features between two groups. Systolic, diastolic, and mean artery 24-hour ambulatory blood pressures in two groups were similar.

Conclusion: Vitamin D deficiency was found to be common in renal transplant patients. Vitamin D status was not found to be associated with blood pressure in renal transplant patient.

Keywords: Hypertension, vitamin D levels, renal transplantation, 24-hour ambulatory blood pressure, graft function

Öz

Amaç: Böbrek transplantasyonu böbrek yetmezliğinin en önde tedavisidir. Renal transplant hastalarında D vitamini eksikliği yaygın görülmektedir. Vitamin D Renin-anjiyotensin-aldosteron sistemi inhibisyonu ile hipertansiyon ve kardiyovasküler hastalıklardan korumaktadır. Bu çalışmadaki amaç, vitamin D düzeyleri ile 24 saatlik ambulatuar kan basıncı ve greft fonksiyonunu etkileyebilecek parametreler (vücut kitle indeksi, açlık plazma glikozu, lipit profili) arasındaki ilişkiyi belirlemektir.

Yöntem ve Gereç: Renal transplant hastalarında klinik parametreler, D vitamini düzeyleri ve kan basıncı arasındaki ilişki karşılaştırıldı. Tüm hastaların kan basıncı seviyeleri 24 saatlik ambulatuar kan basıncı takibi ile değerlendirildi.

Bulgular: Çalışmaya toplam 115 renal transplant hastası alındı. Ortalama D vitamini düzeyi 16,28 ± 5,2ng/ml olup hastaların % 10,4'ünde ciddi vitamin D yetmezliği (<10ng / ml), ve % 70,4'ünde vitamin D eksikliği (10-20ng/ml) saptandı. D vitamini eksikliği (10-20ng/ml) kadınlarda erkeklerden daha sık olduğu bulundu. Çalışmada hastalar iki gruba ayrıldı, birinci gurup vitamin D düzeyi 20 ng/ml'den az olanlar, ikinci gurup vitamin D düzeyi 20 ng/ml'ye eşit ya da daha yüksek olanlar. İki grup arasında yaş, vücut kitle indeksi ve donör özelliklerinde istatistiksel olarak anlamlı fark yoktu. Sistolik, diyastolik ve ortalama 24 saatlik ambulatuvar kan basıncı her iki grupta benzerdi.

Sonuç: D vitamini eksikliği renal transplant hastalarında yaygın olduğu saptandı. Renal transplant hastalarında vitamin D düzeyinin kan basıncı ile ilişkili olmadığı bulundu.

Anahtar Kelimeler: Hipertansiyon, vitamin D, böbrek nakli, 24 saatlik ambulatuvar kan basıncı, greft fonksiyonu

Introduction

Renal transplantation is the treatment of choice for end-stage renal disease. Despite improvement in acute rejection in patients with renal transplantation, the loss of the chronic rejection graft remains unclear [1,2]. The poor results of renal fibrogenic driving forces include endothelial dysfunction, renal intimal proliferation, and renal ischemia related to hypertension (HT) play an important role in this process of accelerating graft loss [2]. In this process, vitamin D may play an important modulatory role in the vascular area for suitable graft function.

Vitamin D is one of the fat-soluble vitamins. The most important function of vitamin D is keeping parathyroid hormone (PTH) together with calcium (Ca) and phosphorous (P) levels in the physiological range, by providing Ca and P absorption in the intestine [3]. Beside the effect of vitamin D on bone and mineral metabolism, it also has non-genomic effects in many tissues that has the vitamin D receptors. In the liver it regulates lipid metabolism and balances insulin levels. Through renin-angiotensin-aldosterone system (RAAS) inhibition, vitamin D has beneficial effect on HT and cardiovascular diseases [4]. Moreover, vitamin D in renal transplant patients may have protective effects in the process of graft loss and occurence of HT. Vitamin D has also been demonstrated to be deficient in renal transplant patients [5].

In line with this evidence we aimed to investigate the relation between vitamin D levels and 24-hour ambulatory blood pressures and parameters that affect graft function include body mass index (BMI), fasting plasma glucose, lipid profile in renal transplantation patients.

Material and Method

This prospective study was conducted at Hacettepe University, Department of Nephrology, with the approval of the local ethics committee. Consecutive renal transplant patients (transplantation date >6 months) over the age of 18 who were under regular follow-up, at our hospital between 15th January to 15th March, were screened for eligibility for inclusion in this study.

In all patients vitamin D levels, serum creatinine, blood urea nitrogen, calcium (Ca), phosphate (P), lipid profiles, alkaline phosphatase (ALP), fasting plasma glucose were measured and at the same time the blood pressure has been followed and the antihypertensive drugs were recorded.

Venous blood sample for biochemical parameters was obtained by venipuncture. Vitamin D level was measured by high sensitivity ECLIA (Electrochemiluminescence Immunoassay) method by using Roche Hitachi Cobas 6000 analyzer. Vitamine D results were given in ng / mL. Vitamin D status was defined as sufficient >30ng/

mL, insufficient 10-20 ng/ml, or deficient <10 ng/mL according to manufacturer's instructions. Moreover, 24-hour ambulatory blood pressure monitoring was performed simultaneously with venous blood sample.

24-hour ambulatory blood pressure readings were taken every 30 minutes during the day and every hour at night. The heart rate were also be measured at the same time. Multiple blood pressure readings were averaged over the 24-hour period to obtain the mean or average blood pressure. Variations in blood pressure and heart rate, the blood pressure distribution pattern, and other statistics were also calculated. HT were defined according to 24-hour ambulatory blood pressure when one or more of these criteria exist; the 24-hour average blood pressure was >130/80 mmHg and the daytime average >135/85 mmHg and/or nighttime average >120/70 mmHg. Also, when blood pressure falls by <10% during nighttime, it was defined as nondipping.

Immunosuppressive therapy, antihypertensive treatment and BMI of renal transplant patients were recorded. Estimated glomerular filtration rate (GFR) was calculated by the Modification of Diet in Renal Disease (MDRD).

In this study, the exclusion criteria included having active infection, liver disease, malignancy and under the 6 six months from the date of transplantation.

All statistical analysis was carried out using SPSS for Windows version 11.5 (SPSS, Chicago, IL). Comparison of parametric and nonparametric data between groups were done using Student's t-test, Mann–Whitney U test and Kruskal Wallis variance analysis, respectively. Results are given as mean ± standard deviation and median (min–max). A p-value of less than 0.05 was considered as statistically significant.

Result

A total of 115 renal transplant recipients (aged 19-74 years) were enrolled in the study. The mean age of the patients was 38.9±12.6, mean BMI 25.67±4.5, mean duration of dialysis 37.35±14 months and mean posttransplant time were 68.2±65.55 months. The demographic characteristics of the study group have been summarized in Table 1.

Table 1. Demographic features of renal transplant patients

Variable	Patients (N:115)
Creatinine (mg / dL)	1.31±0.8
Blood Urea Nitrogen (mg / dL)	21.24±11.6
GFR (mL / min)	78.19±26.49
Calcium (mg / dl)	9.48± 0.63
Phosphorus (mg / dl)	3.36±0.69
Alkaline phosphatase (U / I)	88.4±42.8
24 hour urine Na (mEq / lt)	154.4±64.5
24-hour urine protein (mg / day)	377.1±646
Glucose (mg / dl)	99.85±23.65
Hemoglobin (g / dl)	13.6±1.81
Cholesterol (mg / dl)	193.79±42.85
Triglyceride (mg / dl)	168.1±86
Low density lipoprotein (mg/dl)	113.5±35.17
High density lipoprotein (mg/dl)	57±17.62
Values are given as mean ± standard deviation	

The vast majority etiology of chronic kidney disease were glomerulonephritis and renal disease of unknown aetiology. Most of the patients (%58) had a living donor. Mean level of vitamin D was 16.28±5.2ng/ml, 10.4% of the patients had severe vitamin D insufficiency (<10ng/ml), 70.4% with a level between 10-20 ng/ml, 17.5% between 21-30ng/ml, and the rest (1.7%) had levels more than 30 ng/ml. The vitamin D deficiency (<20ng/ml) was seen more frequently in women than man.

According to the level of vitamin D, patients has been divided into two groups, the first with levels of less than 20 ng/ml, the second one with levels of equal or higher than 20 ng/ml. There were no statistically significant difference in age, BMI and donor features between two groups. Systolic, diastolic, and mean artery blood pressures in two groups were similar. 67.8% of the patients had HT and 37.4% of the cases had using one, 26.1% two and 4.3% three antihypertensive agents. 32.2% of the cases were normotensive. Age, sex, BMI, donor characteristics and blood pressure values of the study groups have been summarized in Table 2.

Table 2. Age, sex, BMI, donor characteristics and blood pressure values of the study population

Parameters	Group 1 (vitamin D <20 ng/ml) (n=93)	Group 2 (vitamin D ≥20 ng/ml) (n=22)	P value
Age (years)†	38.6 ± 11.9	40.2 ± 15.6	>0.05
Gender (Male)Ω	38(55)	3(19)	0.041
BMI (kg/m2) †	25.8 ± 4.5	24.8 ± 4.6	>0.05
Donor (% live) †	60	50	>0.05
Systolic blood pressure (mm/Hg)†	127.7 ± 12.3	124.8 ± 12.9	>0.05
Diastolic blood pressure(mm/Hg)†	79.8 ± 7.9	80 ± 8	>0.05
Mean blood pressure (mm /Hg) †	93.59 ± 9.3	93.54 ± 8.6	>0.05

† Values are given as mean ± standard deviation
Ω Values are given as percentage
* Values are given as median (minimum-maximum)

Laboratory investigations (GFR, creatinine, Ca, P, ALP, C-reactive protein, fasting plasma glucose, hemoglobin, lipid profile) showed no significant difference among two groups (Table 3).

Table 3. Laboratory characteristics of the study population

Parameters	Group 1 (vitamin D <20 ng/ml) (n=93)	Group 2 (vitamin D ≥20 ng/ml) (n=22)	P value
Creatinine (mg / dl)	1.24 ± 0.76	1.58 ± 0.93	>0.05
Blood Urea Nitrogen (mg / dl)	19.7 ± 10.2	27.7 ± 14.8	0,003
Glomerular Filtration Rate (ml / min)	79.9 ± 25.8	70.6 ± 25.5	>0.05
Calcium (mg / dl)	9.43 ± 0.65	9.69 ± 0.47	>0.05
Phosphorus (mg / dl)	3.32 ± 0.67	3.54 ± 0.77	>0.05
Alkaline phosphatase (U / I)	90 ± 46.1	81.5 ± 23.5	>0.05
24 hour urine Na (mEq / lt)	153.17 ± 63.4	159.68 ± 70.1	>0.05
24 hour urine protein (mg / day)	394.2±687.5	305±440.8	>0.05
C-reactive protein (mg / L)	0.57±0.53	0.43±0.38	>0.05
Glucose (mg / dl)	99.47 ± 21.67	101.45 ± 31.21	>0.05
Hemoglobin (g / dl)	13.47 ± 1.78	14.26 ± 1.83	>0.05
Cholesterol (mg / dl)	197.1 ± 44.16	179.8 ± 34.28	>0.05
Triglyceride (mg / dl)	168.1 ± 83.5	168.2 ± 98.38	>0.05
Low density lipoprotein (mg/dl)	115.65 ± 36.83	104.8 ± 25.97	>0.05
High density lipoprotein (mg/dl)	58.4 ± 18.28	51.3 ± 13.39	>0.05

Values are given as mean ± standard deviation

Discussion

Renal transplantation is the leading treatment method in chronic kidney disease. Efforts to extend the graft survival period after kidney transplantation have increased successfully. However, metabolic complications and HT have also been increased. The incidence of HT in kidney transplant cases ranges from 50 to 90% in the literatüre [6-8]. In a study conducted by Paoletti et al. [8] of 94 renal transplant patients (69.1% male) which had monitoring with 24-hour ambulatory blood pressure, only 5% of the patients were normotensive. Also, poor affects of HT in renal transplant patients morbidity and mortality has been demonstrated in the study.

Among the reasons for high rates of HT after transplantation include presence of pre-transplant HT, higher BMI values, characteristics of the donor (elderly, male, hypertensive), prolonged transplantation surgery and allograft ischemia, renal artery stenosis, calcineurin inhibitors and steroids, recurrent or newly developing glomerulonephritis, chronic allograft nephropathy [9]. Understanding pathogenesis of HT in renal transplant patients is crucial for management of the complications, as well as developing efficient treatment regimens.

The positive effects of vitamin D on regulation of blood pressure are known. The molecular effect of vitamin D on RAAS activation is suppression of renin expression by binding of the transcription factor (cAMP-response element-binding protein) to vitamin D receptor (VDR) [10]. Increased RAAS activation was seen in mice that were blocked with VDR and the 1α-hydroxylase system [11]. Additionally, studies have shown that vitamin D and its analogues can decreases renin and angiotensin II levels [12]. Furthermore, vitamin D has also vasculoprotective effect by increasing endothelial nitric oxide synthase, reducing endothelial adhesion molecules and creating anti-inflammatory results [13].

In the present study, only 1.7% of the cases had adequate vitamin D levels above ≥30 ng/ml. Stavroulopoulos and colleagues found that vitamin D deficiency and insufficiency in 509 kidney transplant recipients were present in 85.2%. In renal transplant patients vitamin D insufficiency has been reported between 29% and 43%, deficiency between 56% and 46%, and severe deficieny between 12% and 5% [14]. In a study conducted by Boudville et al. they have found that 75.5% of patients with renal transplant have vitamin D deficiency and insuficiency [15].

Because the vitamin D levels were not sufficient in all of the patients, the patients were divided into two groups: those with vitamin D levels <20ng / ml (80.8%) and those

with ≥20ng / ml (19.2%). This distinction allows the determination of the incidence of vitamin D deficiency and insufficiency and comparison of both groups with other data. This also may have posed limitations in this study. Additionally, no statistically significant difference was observed between the systolic, diastolic and mean blood pressures values, between the two groups (p> 0.05).

Argiles and colleagues investigated the relationship between blood pressures and vitamin D levels in 22 stable hemodialysis patients, and found a significant association between blood pressure and vitamin D levels [16]. While there are conflicting results regarding Vitamin D and HT, our results support the argument that there were no relation with vitamin D and HT in renal transplant patients. Similarly, there were no relation between vitamin D levels parameters (body mass index, fasting plasma glucose, lipid profile) that effect graft function.

This study has several limitations. Patients mostly had vitamin D level below <30ng/ml which limit the variety of the patients. However, these limitations do not hinder the results of the study; rather, they reveal the lack of homogeneity. Furthermore, this was a single-center study and additionally the small sample size may have posed limitations in this study.

In conclusion, vitamin D deficiency is seen in high proportions in kidney transplant patients. Vitamin D level was not found to be associated with blood pressure in renal transplant patient. More studies with a larger sample population are needed to determine whether such an association does in fact exist.

Financial & competing interests disclosure: We are stating that we have no financial and personal relationships with other people or organisations that could inappropriately influence (bias) our work. As a result we have no conflict of interest to report. We hereby declare that we have made a substantial contribution to the information submitted for publication; we have read and approved the final manuscript and the manuscript or portions thereof are not under consideration by another journal.

Declaration of conflicting interests

The author declared no conflicts of interest with respect to the authorship and/or publication of this article.

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