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ASSESSMENT OF ENDOTHELIAL DYSFUNCTION AND VASCULAR STIFFNESS AFTER CHOLECALCIFEROL ACCORDING TO DIALYSIS MODALITY

KOLEKALSİFEROL SONRASI ENDOTEL DİSFONKSİYONU VE DAMAR SERTLİĞİNİN DİYALİZ MODALİTESİNE GÖRE DEĞERLENDİRİLMESİ

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ABSTRACT

Objective: The risk of developing cardiovascular disease (CVD) increases significantly in children with chronic kidney disease (CKD) especially with low serum 25- hydroxyvitamin D (25OHD) levels. Herein; we aimed to compare the effects of vitamin D deficiency and the impact of cholecalciferol treatment on endothelial functions and vascular stiffness in children with CKD receiving hemodialysis (HD), peritoneal dialysis (PD) and non-dialysis (ND).

Methods: HD (n=7), PD (n=7) and ND (n=27) patient groups consisting of 41 children totally with low 25OHD levels were compared among each other in regards of biochemical parameters, flow-mediated dilatation (FMD) and local arterial stiffness before and after a single dose of 300.000 units of cholecalciferol treatment.

Results: There was no difference in FMD and local arterial stiffness values between HD, PD and ND patient groups before vitamin D supplementation. Significant increase in endothelium-dependent FMD was observed in all patient groups after intervention with cholecalciferol; however the improvement in endothelium-independent FMD and local arterial stiffness measurements was demonstrated in patients with PD and ND. Baseline parathormon level was higher in patients on dialysis; at the end of the study, significant decrease was detected only in patient group not receiving dialysis.

Conclusions: Endothelial dysfunction and impaired vascular stiffness were determined in children with CKD with low 25OHD levels regardless of the disease severity. Recovery with cholecalciferol therapy revealed that vitamin D deficiency should be corrected even in early stages of CKD to prevent the development of CVD.

Keywords: Vascular stiffness, endothelial dysfunction, chronic kidney disease, cholecalciferol

ÖZ

Amaç: Özellikle serum 25-hidroksivitamin D (25OHD) seviyeleri düşük kronik böbrek hastalığı (KBH) olan çocuklarda kardiyovasküler hastalık (KVH) gelişme riski önemli ölçüde artmaktadır. Bu çalışmada; KBH olan ve hemodiyaliz (HD), periton diyalizi (PD) ve diyaliz dışı (ND) tedavi alan çocuklarda D vitamini eksikliğinin etkilerini ve kolekalsiferol tedavisinin endotel fonksiyonları ve damar sertliği üzerine olan etkilerini karşılaştırmayı amaçladık.

Yöntem: Serum25OHD düzeyi düşük toplam 41 çocuktan oluşan 7 HD, 7 PD ve 27 ND hasta grupları; 300.000 ünite tek doz oral kolekalsiferol öncesi ve sonrası biyokimyasal parametreler, akım aracılı dilatasyon (FMD) ve lokal arter sertliği açısından kendi aralarında karşılaştırıldı.

Bulgular: D vitamini takviyesi öncesi HD, PD ve ND hasta grupları arasında FMD ve lokal arteryel sertlik değerlerinde farklılık yoktu. Kolekalsiferol tedavisi sonrası tüm hasta gruplarında endotel bağımlı FMD de önemli artış gözlendi; ancak endotel bağımsız FMD ve lokal arteryel sertlik ölçümlerinde iyileşme sadece PD ve ND hastalarında gösterildi. Diyaliz olan hastalarda (HD, PD) başlangıç parathormon düzeyi daha yüksekti; çalışma sonunda ise sadece diyalize girmeyen hasta grubunda anlamlı azalma olduğu tespit edildi.

Sonuç: KBH olan ve 25OHD düzeyi düşük çocuklarda hastalığın şiddetine bakılmaksızın endotel fonksiyon bozukluğu ve artmış damar sertliği saptanmıştır. Kolekalsiferol tedavisi ile gözlenen iyileşme, KVH gelişimini önlemek için D vitamini eksikliğinin KBH nın erken evrelerinde bile düzeltilmesi gerektiğini ortaya koymuştur.

Anahtar Kelimeler: Damar sertliği, endotel disfonksiyonu, kronik böbrek hastalığı, kolekalsiferol

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Introduction

Cardiovascular disease is the leading cause of morbidity and mortality in children with end-stage renal disease (ESRD).[1] Hypertension, disturbed calcium-phosphorus metabolism, elevated serum intact parathyroid hormone (iPTH) and dysregulated renin-angiotensin-aldosterone axis have been associated with cardiac dysfunction and increased vascular stiffness in chronic kidney disease (CKD) patients.[2] Left ventricular hypertrophy, systolic or diastolic dysfunction have been detected even in early stages of renal impairment.[3]

Endothelial dysfunction as an initial sign of atherosclerotic process has also been demonstrated in children with early stages of CKD.[4] Flow-mediated dilatation (FMD) of the brachial artery which has been validated to assess endothelial dysfunction and determination of an increased carotid intima media thickness (cIMT) have been used as an indicator for cardiovascular events in patients with CKD.[5,6]

Previous studies revealed that low level of serum 25-hydroxyvitamin D3 (25OHD) in CKD patients has been associated with higher cardiovascular mortality,endothelial dysfunction and increased arterial stiffness.[7,8] In recent years, vitamin D has been demonstrated to prevent ventricular hypertrophy,suppress vascular smooth muscle cell proliferation and inhibit systemic inflammation in CKD.[9-11] As vitamin D deficiency has been reported to be more prevalent in this population,especially in patients on peritoneal dialysis, prompt vitamin D supplementation is crucial for improved cardiovascular status.

In the present study, we evaluated the efficacy of oral cholecalciferol on left ventricular hypertrophy, arterial stiffness and brachial artery FMD, in addition to the markers of inflammation and calcium-phosphorus metabolism and we compared the results between hemodialysis (HD), peritoneal dialysis (PD) and pre-dialysis patients.

Methods

Patients

Serum 25OHD levels of forty-four children with CKD including those on dialysis therapy who had been followed up by the department of pediatric nephrology were investigated. Its levels were classified according to the KDOQI Guidelines. Serum 25OHD levels between 16 and 30 ng/ml were described vitamin D insufficiency, while <15ng/ml and <5 ng/ml deficiency and severe deficiency, respectively.[12] The study protocol was approved by University Ethics Committee in accordance with the Declaration of Helsinki. Written informed consent for participation was taken from all patients and/or their parents.

Patients who had sufficient serum vitamin D levels (25OHD>30 ng/ml), inflammation, heart disease, hepatic disease and malignancy were excluded from the study.

Of the 44 patients with CKD, 41 patients with low vitamin D levels were recruited for the study.

Laboratory

After a fasting period of at least 8 hours, venous blood samples were obtained. At baseline, serum creatinine, urea nitrogen (BUN), glucose, albumin, calcium, phosphorus, alkaline phosphatase (ALP), total cholesterol, triglyceride, low-density lipoprotein (LDL), high-density lipoprotein (HDL), iPTH and 25OHD were measured. C-reactive protein (CRP) and fibrinogen were evaluated for inflammatory status. All the blood samples were collected one day before hemodialysis session.

Echocardiography

All children with CKD underwent 2-D M-mode echocardiography using a Vivid 7 system (GE Vingmed, UltrasoundAS, Horten, Norway) with a 3 MHz transducer. The cardiovascular assessment was performed by an experienced pediatric cardiologist after the subjects had rested for at least 10 minutes and the parameters were estimated according to guidelines of American Society of Echocardiography.[13] Left ventricular mass index (LVMI) was calculated with the formula described by De Simone et al.[14] Left ventricular hypertrophy was defined as LVMI greater than 38.6 g/$m^{2.7}$.

Flow-Mediated Dilatation

Flow-mediated, endothelium-dependent vasodilatation was performed by the same physician for fasting subjects in a quiet room. Caffeine and exercising for at least 8 hours were avoided. After 10 minutes of resting period, B-mode ultrasound images were obtained using 10 MHz linear array according to the method that was described by Celermajer et al.[15] Firstly, diameter of the right brachial artery was measured on antecubital fossa. After the placement of a pneumatic tourniquet above the cubital region, it was inflated to a pressure of 300 mmHg for 5 minutes. The diameter of the brachial artery was obtained again for reactive hyperemia, 45-60 seconds after the cuff deflation. Fifteen minutes later, it was remeasured for basal and for 5 minutes after 400 µg sublingual glyceryltrinitrate.

Distensibility

Distensibility of carotid arteries is a sensitive marker for the functional changes of vascular tree which predicts cardiovascular disease (CVD) risk earlier than increased cIMT. It is defined with distensibility coefficient (DC), stiffness index (β), incremental elastic modulus (E_{inc}) and determines local arterial stiffness.[16]

A pediatric cardiologist who was blinded to the patients' clinical situation performed echocardiography and vascular ultrasound. Intraobserver coefficient of variation was 2.1% for FMD.

Intervention

After initial assessments of biochemical and cardiovascular results, 41 children with CKD having low 25OHD levels (<30 ng/ml) were given single dose of 300.000 IU oral cholecalciferol. All laboratory tests and cardiovascular measurements were repeated after 12 weeks. The effects of vitamin D supplementation were compared between HD, PD and pre-dialysis patients.

Statistical Analysis

Mean ± standart deviation was used for continuous and normally distributed variables, median for skewed variables. One-way ANOVA or Kruskall-Wallis test was performed for the comparison of multiple categories. Significant difference before and after cholecalciferol was calculated with paired *t*test or Wilcoxon test. Statistical analysis was performed using Statistical Package for the Social Sciences version 22.0 software (IBM Corp.; Armonk, NY, USA) and p value of 0.05 or lower was significant.

Results

Patient Characteristics

Forty-four CKD patients (24 girls) were screened. Forty-one of 44 children (93.2%) had low levels of serum 25OHD. Of the 41 patients, median age was 14.9 years (10.9-16.5). 13 of them (31.7%) had vitamin D insufficiency and 28 (68.3%) had deficiency. Severe deficiency was found in 5 patients (12.2%). The patients were grouped according to their dialysis modality such as HD (n=7), PD (n=7) and pre-dialysis groups (n=27). All of the HD patients were dialyzed for 3-4 hours thrice weekly using bicarbonate based dialysate and all PD patients received automated peritoneal dialysis. During the study period, 21 patients (51.2%) were treated with calcium-based phosphate binders whereas 8 patients (19.5%) with sevalemer. Calcitriol was prescribed for 16 children. There were no differences with regards to age, gender, duration of kidney disease, time on dialysis and BMI between HD, PD and pre-dialysis groups. The mean duration of dialysis were 2.93±2.48 and 4.3±3.15 years, in HD and PD patients, respectively (p=0.38). Table1 summarizes demographic characteristics of the patients. Mean glomerular filtration rate (GFR) of the children in pre-dialysis group was significantly higher than those in HD and PD groups (p<0.001). Baseline systolic blood pressure did not differ among the groups but diastolic blood pressure was significantly higher in HD patients when compared to others (p=0.046). No significant change was observed in blood pressure values after cholecalciferol supplementation.

Vitamin D and Bone Mineral Metabolism

Baseline mean serum 25OHD levels were similar in HD (12.6±8.3 ng/ml), PD (9.9±5.5 ng/ml) and pre-dialysis patients (13.1±5.48 ng/ml) (p=0.46). No significant differences were observed in baseline values of serum calcium, phosphorus, calcium-phosphorus product, albumin and LDL-cholesterol between the study groups. The patients in HD and pre-dialysis groups had significantly higher ALP levels than those in PD group (p=0.007). Serum iPTH levels were significantly elevated in HD group when compared to the patients in pre-dialysis group (p=0.034) (Table1). After the supplementation of vitamin D, 25OHD increased significantly in each group. Serum 25OHD levels increased from10.9 to 27.6 ng/ml (p=0.028), 9.9 to 21.9 ng/ml (p=0.043) and 13.1 to 32.8 ng/ml (p<0.001) in HD, PD and pre-dialysis patients, respectively (Figure 1) No significant change was observed in calcium, phosphorus, calcium-phosphorus product, albumin and LDL-cholesterol levels in either groups before and after cholecalciferol treatment. However, significant decreament in ALP and iPTH levels were detected only in pre-dialysis patients. Mean ALP levels decreased from 238.2 to 184.5 U/l (p=0.003) and median iPTH decreased from 200.4 to 127.3 pg/ml (p=0.005). There was a trend towards a decline in ALP and iPTH in HD and PD groups that was not significant.

Endothelial and Inflammatory Markers

Both median CRP (0.66 mg/dl vs 0.12 mg/dl, p=0.04) and mean fibrinogen values (4.6±0.9 g/l vs 3.75±0.8 g/l, p=0.035) significantly elevated in HD group when compared with pre-dialysis group. However, no change was observed in CRP and fibrinogen levels among the groups following cholecalciferol supplementation. Regarding the indicators for endothelial dysfunction, baseline endothelium-dependent (p=0.42) and independent FMD measurements (p=0.54) were similar between patients having HD, PD and no replacement therapy. After vitamin D treatment, there was a significant increase in mean endothelium-dependent FMD from 5.58% to 7.85% (p<0.001), 5.7% to 8.5% (p=0.016) and 7.23% to 9.77% (p<0.001) in HD, PD and pre-dialysis patients, respectively. Although mean endothelium-independent FMD improved significantly in PD (12.48±5.81% vs 13.4±5.26%, p=0.036) and pre-dialysis groups (13.99±4.96% vs 15.38±5.18%, p=0.022) after cholecalciferol supplementation, the increase in HD patients from 12.05±2.21% to 12.77±1.95% did not reach statistical significance (p=0.14) (Table 2).

Cardiac Function

Patients on HD had significantly higher mean LVMI than those in pre-dialysis group (59.1±34.6 vs39.4±11.7 g/$m^{2.7}$, p=0.04). Eventually, vitamin D therapy had no effect on LVMI within the study groups.

Carotid Artery Structure and Function

DC, β and E_{inc} values of both CCA were similar between HD, PD and pre-dialysis patients. Following vitamin D treatment, significant improvement was observed in DC, β and E_{inc}values of the patients in PD and pre-dialysis groups whereas no recovery was noted in hemodialyzed children (Table 3-4).

Table 1. Baseline demographic, biochemical and cardiovascular parameters

	HD (n=7)	PD (n=7)	Nondialysis (n=27)	p value
Age, years	15.1±1.6	15.2±3.3	12.9±4.2	NS
Height SDS	-4.62* (-8.81 --2.67)	-1.76 (-3.93 -1.13)	-1.63 (- 3.8 - 0.67)	0.034
BMI	19.34±7.46	17.52±3.61	18.1±2.86	NS
BMI SDS	0.86±3.63	- 0.41±1.56	0.32±1.2	NS
Duration of CKD, years	6.22±2.93	4.42±3.04	4.52±3.12	NS
SBP, mmHg	120(107-155)	120(96-120)	107(100-120)	NS
DBP, mmHg	81.86±23.54**	62.57±13.26	67.52±12.7	0.046
Creatinin (mg/dl)	5.21 (4.6-7.19)*	5.69(5.53-9.12)*	1.64(1.18-3.18)	0.000
eGFR (ml/min/1.73m^2)	14.11±3.67*	14.08±5.35*	46.45±24.43	0.000
25OHD (ng/ml)	12.6±8.39	9.91±5.54	13.13±5.48	NS
iPTH (pg/ml)	531.6(238.9-945)*	229.4(109.2-323.3)	200.4(111.7-387)	0.034
Calcium (mg/dl)	9.8(9-10.1)	9.7(9-9.9)	9.5(9.2-9.8)	NS
Phosphorus (mg/dl)	4.9(4.7-5.4)	4.3(3.1-5.6)	4.5(4.2-4.8)	NS
Ca x P product	47.9±6.2	41.6±15	41.8±6.4	NS
Total cholesterol (mg/dl)	167(144-230)	189(175-203)	168(143-192)	NS
LDL cholesterol (mg/dl)	91.1±34	112.6±27.3	96.1±31.8	NS
CRP (mg/dl)	0.66(0.29-1.97)*	0.07(0.03-0.56)	0.12(0.05-0.34)	0.04
Fibrinogen (g(l)	4.6±1.32*	4.58±0.9*	3.75±0.83	0.035
LVMI (gr/m$^{2.7}$)	59.15±34.61*	41.72±12.44	39.48±11.79	0.04
RCCA				
DC (kPa^{-1}10^{-3})	42.07±11.82	52.31±25.99	53.9±20.67	NS
β	3.99±1.53	4±1.55	3.53±1.22	NS
E_{inc} (kpa 10^3)	0.31±0.09	0.26±0.1	0.24±0.09	NS
LCCA				
DC (kPa^{-1}10^{-3})	42.24±10.97	49.41±20.37	54.33±21.24	NS
β	3.91±1.43	4.22±1.96	3.57±1.48	NS
E_{inc} (kpa 10^3)	0.27±0.08	0.27±0.11	0.24±0.10	NS
ED - FMD (%)	5.58±2.09	5.70±4.19	7.23±3.8	NS
EI - FMD (%)	12.05±2.21	12.48±5.81	13.99±4.96	NS

Data are expressed as mean±SD and median (interquartile range)

HD hemodialysis, *PD* peritoneal dialysis, *SDS*standart deviation score, *BMI* body mass index, *CKD* chronic kidney disease, *SBP* systolic blood pressure, *DB*diastolic blood pressure, *eGFR* estimated glomerular filtration rate, *25OHD* 25-hydroxyvitaminD, *iPTH* intact parathyroid hormone, *LDL* low-density lipoprotein, *CRP*: C-reactive protein, *LVMI* left ventricular mass index, *RCCA* right common carotid artery, *LCCA* left common carotid artery, *DC*distensibility coefficient, *β* stiffness index, E_{inc}elasticity increment model, *ED-FMD* endothelium-dependent flow-mediated dilatation, *EI-FMD* endothelium-independent FMD, *NS* not significant.

* p<0.05 vs nondialysis; ** p<0.05 vs PD and nondialysis

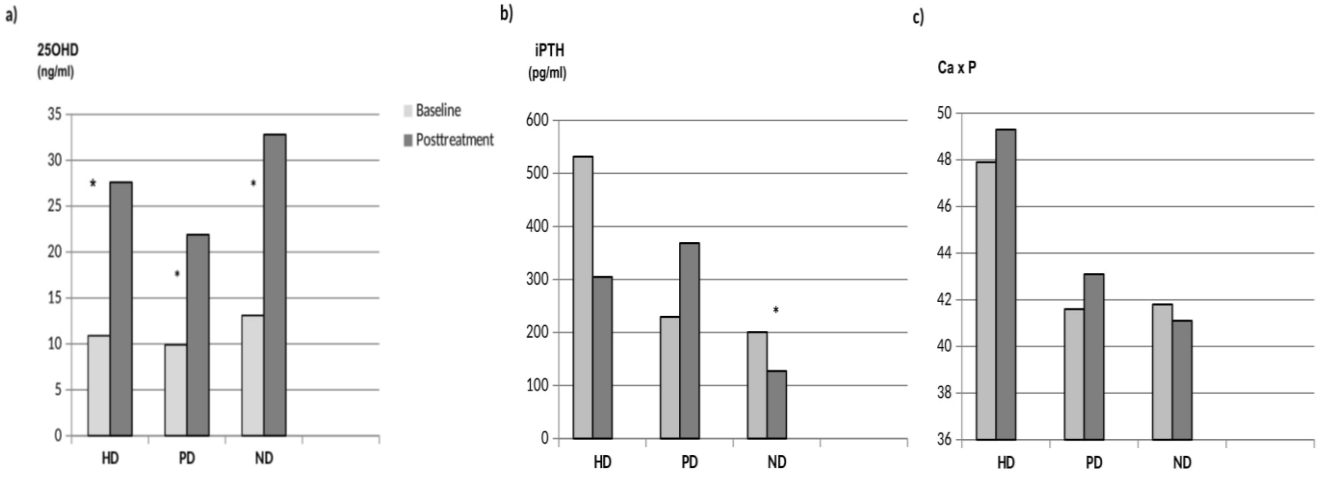

Figure 1. Changes in median 25-hydroxyvitamin D (25OHD), intact parathyroid hormone (iPTH) and in mean calcium phosphorus product (Ca x P) values in children with hemodialysis (HD), peritoneal dialysis (PD) and nondialysis (ND) before and after cholecalciferol. * p<0.05

Table 2. Cardiovascular measurements in hemodialysis patients before and after cholecalciferol

	Baseline	Post-treatment	p value
RCCA			
DC ($kPa^{-1}10^{-3}$)	42(31.5-55.8)	41.9(27.7-68.6)	NS
β	3.99±1.53	4.2±2.18	NS
E_{inc} (kpa 10^3)	0.31±0.09	0.29±0.14	NS
LCCA			
DC ($kPa^{-1}10^{-3}$)	42.224±10.97	47.26±16.89	NS
β	3.91±1.43	3.8±1.3	NS
E_{inc} (kpa 10^3)	0.27±0.08	0.26±0.1	NS
ED - FMD (%)	5.58±2.09	7.85±2.2	0.000
EI - FMD (%)	12.05±2.21	12.77±1.95	NS

RCCA right common carotid artery, *LCCA* left common carotid artery, *DC*distensibility coefficient, *β* stiffness index, E_{inc} elasticity increment model, *ED-FMD* endothelium-dependent flow-mediated dilatation, *EI-FMD* endothelium-independent FMD, *NS* not significant.
p<0.05 statistical significance

Table 3. Cardiovascular measurements in peritoneal dialysis patients before and after cholecalciferol

	Baseline	Post-treatment	p value
RCCA			
DC ($kPa^{-1}10^{-3}$)	52.3(25.9-75.8)	61.8(49.6-68.5)	NS
β	4±1.55	2.78±0.85	0.044
Einc (kpa 10^3)	0.26±0.1	0.2±0.06	0.043
LCCA			
DC ($kPa^{-1}10^{-3}$)	49.41±20.37	64.73±18.37	0.017
β	4.22±1.96	2.74±0.92	0.016
E_{inc} (kpa 10^3)	0.27±0.11	0.19±0.06	0.014
ED - FMD (%)	5.70±4.19	8.5±3.56	0.016
EI - FMD (%)	12.48±5.81	13.4±5.26	0.036

RCCA right common carotid artery, *LCCA* left common carotid artery, *DC*distensibility coefficient, *β* stiffness index, E_{inc} elasticity increment model, *ED-FMD* endothelium-dependent flow-mediated dilatation, *EI-FMD* endothelium-independent FMD, *NS* not significant.
p<0.05 statistical significance

Table 4. Cardiovascular measurements in nondialyzed patients before and after cholecalciferol

	Baseline	Post-treatment	p value
RCCA			
DC ($kPa^{-1}10^{-3}$)	52.75(38.09-60.19)	55.66(45.56-74.39)	0.029
β	3.53±1.22	3.2±1.05	NS
E_{inc} (kpa 10^3)	0.24±0.09	0.21±0.07	0.047
LCCA			
DC ($kPa^{-1}10^{-3}$)	54.33±21.24	57.9±21.83	NS
β	3.57±1.48	3.5±1.1	NS
E_{inc} (kpa 10^3)	0.24±0.10	0.22±0.08	NS
ED - FMD (%)	7.23±3.8	9.77±3.88	0.000
EI - FMD (%)	13.99±4.96	15.38±5.18	0.022

RCCA right common carotid artery, *LCCA* left common carotid artery, *DC*distensibility coefficient, *β* stiffness index, E_{inc} elasticity increment model, *ED-FMD* endothelium-dependent flow-mediated dilatation, *EI-FMD* endothelium-independent FMD, *NS* not significant.
p<0.05 statistical significance

Discussion

Considering that cardiovascular events are the most frequent causes of death in children with CKD, it should be aimed to review and eliminate risk factors with early interventions.[17,18] In the present study, we found remarkable improvement in ED-FMD after cholecalciferol supplementation in children with hemodialysis, peritoneal dialysis and pre-dialysis groups.

FMD as a surrogate marker for endothelial dysfunction has been associated with obesity, hypercholesterolemia and low 25OHD levels.[19] It has also been reported that deterioration in endothelial function begins even in the milder stages of CKD.[4] Decreased nitric oxide bioactivity by reduced synthesis or inhibition via endogenous substances have been shown to contribute to this process.[20,21] After cholecalciferol, we observed statistically significant improvement in ED-FMD value, along with a significant increase in low 25OHD levels in hemodialysis, peritoneal dialysis and pre-dialysis groups whose age, gender, BMI, systolic, diastolic pressure measurements, serum calcium, phosphorus, calcium-phosphorus product, LDL-cholesterol and 25OHD levels

were not statistically different among each other before and after cholecalciferol therapy.

In adult patients having grade 3-4 CKD; Chitalia et al reported improved brachial artery FMD with two doses of 300.000 units of cholecalciferol although changes in pulse wave velocity and augmentation index predicting central arterial stiffness did not reach statistical significance.[22]

Arterial stiffness seen with increased frequency due to aging and hypertension enhance pre-existing CVD and mortality risk in CKD patients because of the alterations of mineral metabolism, hyperparathyroidism, microinflammation, overactivity of sympathetic system and renin-aldosterone axis, abnormalities of nitric oxide system and arterial wall calcification.[17,23,24] Moreover, London et al and Shroff et al have demonstrated increased vascular stiffening in dialyzed adults and children having low 25OHD.[5,25]

Although it was reported that central arterial stiffening increases as kidney functions worsen, similar to Patange et al, who had also revealed 25OHD as a risk factor for vascular stiffness in children receiving hemodialysis; we did not find a difference between hemodialysis, peritoneal dialysis and pre-dialysis groups about DC, Einc and β values indicating our patients' severely affected local arterial stiffening.[8] Therefore, these results which allow us to predict the development of CVD and mortality risk, were demonstrated to be equally impaired in all stages of kidney disease regardless of glomerular filtration rate and it was an important finding revealing that cardiovascular health began to deteriorate even from the initial phase of kidney damage. However significant amelioration in these parameters after 25OHD treatment were only detected in peritoneal dialysis and pre-dialysis groups when compared to hemodialysis patients.

Consistent with a double-blind, randomized study by Marckmann et al who had reported lowered iPTH in non-HD patients compared to HD group after cholecalciferol; decrease of iPTH levels in our study group was significantly detected only in pre-dialysis patients.[26] Thus, it was emphasized the effectiveness of nutritional vitamin D use in mild to moderate CKD for preventing secondary hyperparathyroidism. Regarding its effects on cardiomyocytes and elevated blood pressure resulting in cardiac hypertrophy, iPTH monitorisation is also essential to reduce CVD risk in CKD.[2]

Our study failed to demonstrate any significant change in LVMI, CRP and fibrinogen values among each group after 25OHD intake; whereas in HD patients as expected, it has been shown to have raised levels of these markers at baseline assessment compared to others. The chronic inflammatory environment, caused by the release of cytokines which are increased in the process of CKD, has been associated with cardiac calcification and arteriopathy.[21,27] There are conflicting results about the efficacy of nutritional vitamin D on inflammatory status in CKD. Kalkwarf et al described negative association between CRP and 25OHD levels in 182 children and adolescents with CKD in the age of 5 to 21 years.[28] In this context, Stubbs et al reported a favourable decline in IL-6 levels in seven HD patients after cholecalciferol use.[11] Conversely, in one study conducted with 54 CKD patients older than 18 years of age, no impact of vitamin D supplementation given 40.000 units per week for 8 weeks was observed on inflammatory indicators.[26] Their results were consistent with our data.

In addition to its classical role on bone mineral metabolism, vitamin D has also anti-inflammatory properties,suppresses cardiac hypertrophy,inhibits vascular muscle cell remodeling and renin aldosteron axis.[27,29] Widespread distribution of vitamin D receptors along various cells including endothelium, lymphocytes, vascular smooth muscle cells and myocardium explains the possible mechanisms for preventing the development of CVD.[30]

FMD and local arterial stiffness predicting high CVD and mortality, were found to be severely and equally affected in HD, PD and pre-dialysis groups. Despite the lack of any change within variables that may affect vascular stiffening throughout the study, significantly improved ED-FMD in all groups and decreased arterial stiffness in PD and pre-dialysis groups only with vitamin D intake could be explained by the effects of vitamin D on endothelial and vascular smooth muscle cells.

The failure of significant improvement in EI-FMD, local arterial stiffness and LVMI in hemodialysis patients after intervention may be explained by the prevalent chronic inflammation or other predisposing factors not yet fully elucidated.

The limitations of our study are small sample size, lack of 1,25-hydroxyvitaminD measurements and using only CRP and fibrinogen as proinflammatory markers.

In conclusion; low 25OHD levels in CKD children, may contribute further to the endothelial dysfunction and arterial stiffness which are already present since the early stages of kidney disease. Therefore, intervention with nutritional vitamin D can be considered as a good option in preventing the increased CVD and mortality risk in patients with CKD. Larger randomized trials are needed to confirm these findings.

Compliance with Ethical Standards

Ethical approval was granted by Kocaeli University Ethics Committee with the approval number of 11-6/5-18032014.

Conflict of Interest

The authors declare no conflict of interest.

Author Contribution

MBA: Study design; MAO, KD, MD and OK: Material preparation, data collection and analysis; MBA: Writing first draft of the article; MBA and KB: Critical review of the article, finalization and publication process. All authors read and approved the final version of the manuscript.

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None.

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