Arterial stiffness and 25-hydroxyvitamin D levels in chronic kidney disease patients

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Summary

Objective: Arterial stiffness refers to arterial wall rigidity, particularly developing in central vessels. Arterial stiffness increases in early stage chronic kidney disease (CKD), and it is a strong predictor of cardiovascular and all cause mortality. Vitamin D has beneficial effects on blood pressure, vascular endothelial function and arterial stiffness. 25-hydroxyvitamin D (25(OH)D) deficiency is quite common worldwide and in the CKD population. We aimed to evaluate the prevalence of 25(OH)D deficiency and its relation with arterial stiffness in CKD.

Method: Our study included 101 patients (51 male, 50 female), with stages 3B–5 CKD not on dialysis. A single-cuff arteriograph device (Mobil-O-Graph) was used to evaluate arterial stiffness parameters of pulse wave velocity (PWV) and augmentation index (Alx@75). The patients were divided into two groups: group I vitamin D non-deficient [25(OH)D > 15 ng/mL] and group II vitamin D deficient [25(OH)D ≤ 15 ng/mL].

Results: Overall, the mean 25(OH)D level was 14.1±7.9 ng/mL and 70 patients (69.4%) were vitamin D deficient. The mean Alx@75 value was significantly higher in group II (28.6±10.8% vs. 23.3±13.5%, p=0.038). PWV was higher in group II, but the difference was not significant. Group II exhibited significantly lower serum albumin (p<0.001), hemoglobin (p=0.005), calcium (p=0.041) and estimated glomerular filtration rate (eGFR) (p=0.041), but significantly higher 24-hour proteinuria (p=0.011) and more females (p=0.006). Vitamin D was negatively correlated with Alx@75 augmentation pressure, parathyroid hormone, proteinuria and body mass index, and positively correlated with albumin, hemoglobin, eGFR, calcium and transferrin. 25(OH)D was independently associated with Alx@75 (beta=-0.469, p=0.001) and albumin (beta=0.447, p=0.002).

Conclusion: In CKD patients 25(OH)D deficiency was common, particularly in females. Level of 25(OH)D was independently associated with Alx@75.

Keywords: chronic kidney disease, vitamin D, vascular stiffness, pulse wave analysis.

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Introduction

Arterial stiffness is a term used to define the viscoelastic properties of the vessel wall and refers to arterial wall rigidity.[1] Ageing of the arterial system, progressive structural changes, disintegration and degeneration of elastin, collagen deposition, arterial wall thickening, endothelial damage and progressive arterial dilatation are all associated with arterial stiffness.[2,3] Deterioration of coronary perfusion and left ventricular hypertrophy secondary to arterial stiffness increase morbidity and mortality.[1,3,4] Cardiovascular events and cardiovascular mortality increase in the early stage of chronic kidney disease (CKD). Arterial stiffness is an independent predictor of cardiovascular disease in CKD.[5-7] Increase in arterial stiffness emerges before atherosclerosis and has been evaluated as an early marker of systemic atherosclerosis. Arterial stiffness is independently associated with cardiovascular events and all-cause mortality.[4,6]

Vitamin D deficiency is quite common worldwide affecting approximately 30-50% of the global population,

and measuring 25-hydroxyvitamin D (25(OH)D) is the best method for determining vitamin D deficiency due to its longer half-life.[8-10] Values of 25(OH)D above 30 ng/mL are considered normal.[8,10,11] Vitamin D plays a crucial role in bone and calcium metabolism. In addition, it has beneficial effects on the immune system, blood pressure regulation, vascular endothelial function, and body growth and development.[9,10,12] Previous studies have demonstrated the association between 25(OH)D deficiency and increased arterial stiffness in chronic diseases such as lupus, diabetes, hyperparathyroidism, and kidney disease.[13-15]

Pulse wave velocity (PWV) and augmentation index normalized with 75/min heart rate (Alx@75) are considered to be gold standard index for arterial stiffness.[1,3,6] Al Mheid et al.[16] demonstrated that 25(OH)D levels negatively correlated with PWV and Alx in healthy subjects, and reported that vitamin D deficiency increased arterial stiffness effecting by vascular dysfunction.

In our study, we aimed to evaluate the prevalence of 25(OH)D deficiency and the relationship between 25(OH)D and PWV, and Alx@75 in patients with stage 3B-5 CKD.

Method

One hundred and one (101) patients over 18 years of age with stage 3B-5 CKD not on dialysis, diagnosed by using the specified in the KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease[17] were recruited. Patients were excluded from the study if they were known to have coronary artery disease, heart failure, valvular heart disease, metal valves, stents, metal prosthesis, peripheral artery disease, malignancy, active autoimmune disorders, recent acute coronary syndrome (within the last three months), or if already on vitamin D supplementation. The study was conducted during winter (December through March) throughout the years 2012-2015. Our study was conducted in accordance with the Helsinki declaration, and was approved by the local ethics committee of clinical research (decision number 2016/870, dated 12.05.2016). The patients were informed about the nature of the study, and informed consent was obtained from all participants before entering the study.

All patients underwent a physical examination that included height and weight measurements, age, sex, and etiology of CKD as recorded in the medical chart of each patient. Body mass index was calculated by dividing body weight (kg) by the square of the body height (m^2).

Study group

Vitamin D insufficiency was defined as serum 25(OH)D levels of between 15-30 ng/mL, and deficiency as lower than 15 ng/mL, according to the NKF/KDOQI guidelines.[11] Patients were divided in two groups according to their vitamin D levels: group I vitamin D non-deficient, had 25(OH)D > 15 ng/mL; group II vitamin D deficient, had 25(OH)D ≤ 15 ng/mL.

Biochemical and 25(OH)D measurements

Twelve-hour fasting blood samples were obtained in order to assess serum creatinine, urea, glucose, albumin, uric acid, calcium, phosphorus, parathyroid hormone, 25(OH)D and hemoglobin levels at the time of arterial stiffness measurement. 25(OH)D measurement was performed by radioimmune assay (RIA) method. All hormonal and biochemical tests were measured by Architect c8000 Clinical Chemistry Analyzer device (©2015 Abbott Laboratories. Abbott Park, Illinois, USA). Estimated glomerular filtration rate (eGFR) calculated by the short Modification of Diet in Renal Disease (MDRD) formula.

Arterial stiffness measurement

Arterial stiffness measurements were performed using the oscillometric method. After 15 minutes of rest, measurements were performed with a single-cuff arteriograph device (Mobil-O-Graph PWA, a model pulse wave analysis device, I.E.M. GmbH, Stolberg, Germany). An appropriate blood pressure cuff was placed on the brachial artery trace of the upper arm. The arteriograph device performed three consecutive measurements automatically at 30-sec intervals. The arteriograph measures the blood pressure in the upper arm; then, the device inflates the pressure cuff to 35 mmHg above the systolic blood pressure. This enables detection of fluctuations in brachial artery pressure. A tonometric sensor amplifies the fluctuations and transmits them to the arteriograph. The device software program decomposes early and late systolic and diastolic waves. Pulse wave velocity, pulse pressure, central systolic – diastolic pressure calculated by the central pressure changes, early (direct, P1), late (backward, P2) systolic and diastolic waves. Augmentation pressure is the difference between the first and second systolic peak, and Alx is calculated as the proportion of augmentation pressure to pulse pressure. Augmentation index was normalized to a heart rate of 75 bpm (AIx@75) for comparison for different heart rates.[3,18]

Statistical analysis

Statistical analyses were carried out using the Statistical Package for Social Sciences for Windows, version 17 (SPSS Inc., Chicago, IL, USA). Kolmogorov-Smirnov test was used to determine the normality of the variables' distribu-

tion. Qualitative variables were expressed as number and percentage. The quantitative normally distributed variables were expressed as mean±standard deviation. Abnormally distributed variables were expressed as median and 25th-75th percentiles. Chi-square test was used for comparison of qualitative variables. For intergroup comparisons of quantitative variables, Student's t-test and Mann-Whitney U test were used for data with normal and abnormal distributions, respectively. A Kruskal-Wallis test was used to make comparisons between CKD stages. Normally distributed variable associations were analyzed by Pearson's correlation coefficient and variables with abnormal distributions were analyzed by Spearman's correlation coefficient. Multiple regression analysis was used to determine the factors affecting 25(OH)D and Alx@75 variables. A value of $p<0.05$ was considered significant.

Results

One hundred and one (101) CKD patients who were not on dialysis were included in the study. The mean age was 56.7±11.3 years, 49.5% were female. The mean 25(OH)D level was 14.1±7.9 ng/mL. Out of the 101 analyzed patients, 70 (69.4%) had deficient levels of 25(OH)D, 25 (24.7%) had insufficient levels of 25(OH)D and only six (5.9%) had normal 25(OH)D levels (above 30 ng/mL). Levels of 25(OH)D in CKD stages 3B, 4 and 5 expressed as median and 25th-75th percentile range were: stage 3B: 13.45 ng/mL (10.57-19.95); stage 4: 11.40 ng/mL (8.50-17.80); and stage 5: 9.55 ng/mL (7.40-14.42). Decreased levels were observed in all CKD stages, with a tendency to decrease as the CKD stage increased ($p=0.090$). Distribution of 25(OH)D according to CKD stages is shown in Figure 1.

The CKD patients were grouped as follows based on their 25(OH)D levels: 31 patients (30.6%) in group I [25(OH)D > 15 ng/mL] and 70 patients (69.4%) in group II [25(OH)D ≤ 15 ng/mL]. The causes of kidney disease in group I and group II were diabetes mellitus at 19.4-25.7%, hypertension at 41.9-31.4% and glomerulonephritis at 16.1-11.4%, respectively. In group I, 50% of the diabetic patients were using insulin and 50% were using oral antidiabetic drugs, and in group II 66.7% of the diabetic patients were using insulin and 33.3% were using oral antidiabetic drugs. In all, 64.5% of group I and 52.9% of group II were using a single antihypertensive. Use of antihypertensive drugs is shown in Table 1.

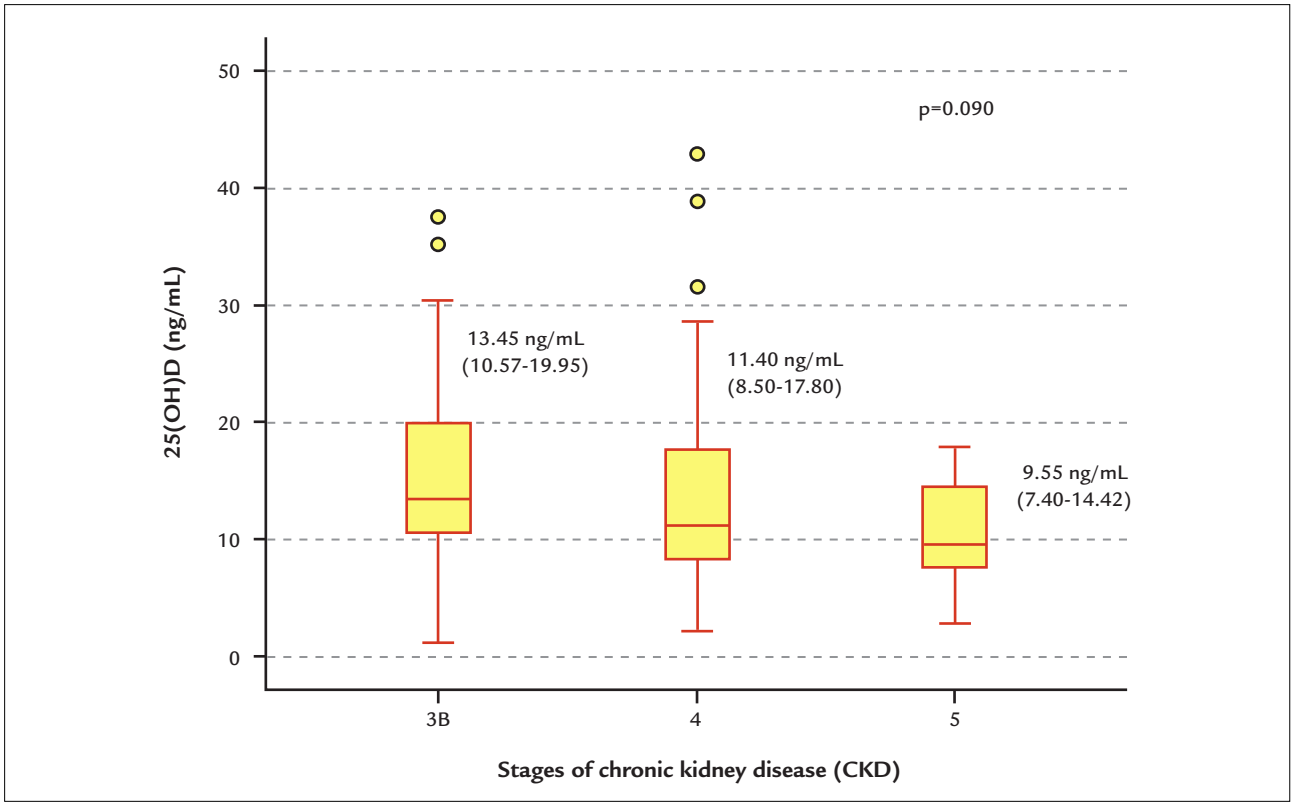

FIGURE 1 25-hydroxyvitamin D levels in chronic kidney disease stages 3B, 4 and 5.
[25(OH)D; median (25-75 percentile)±min, max value]

TABLE 1 Comparison of clinical and biochemical characteristics of groups.

Parameter	Group I [25(OH)D > 15 ng/mL]	Group II [25(OH)D ≤ 15 ng/mL]	p
Female / Male (n)	9 / 22	41 / 29	0.006
Age (year)	55.8±12.8	57.1±10.6	0.591
BMI (kg/m^2)	26.4±3.5	28.0±5.7	0.152
Glucose (mg/dL)	113.1±48.1	103.4±30.4	0.225
Creatinine (mg/dL)	2.64±0.89	3.08±1.76	0.195
eGFR (ml/min/1.73 m^2)	27.5±8.7	23.4±9.4	0.041
Albumin (g/dL)	3.9±0.2	3.5±0.6	<0.001
Uric acid (mg/dL)	8.1±2.1	7.6±2.1	0.375
Calcium (mg/Dl)	9.2±0.6	8.8±0.9	0.041
Phosphorus (mg/dL)	3.65±0.84	4.15±1.34	0.060
ALP (U/L)	101.8±52.4	87.2±34.1	0.254
PTH (pg/mL)	175.1 (81.3-287.6)	200.7 (129.9-315.7)	0.117
Hemoglobin (g/dL)	11.9±1.3	10.9±1.8	0.005
Ferritin (µg/dL)	65.2 (34.2-129.2)	103.1 (40.9-187.7)	0.183
Transferrin (mg/dL)	208.0±46.7	178.4±48.5	0.079
Proteinuria (g/day)	396.8 (213.0-910.0)	895.1 (332.3-1835.9)	0.011
PWV (m/sec)	8.09±1.74	8.25±1.47	0.650
Alx@75 (%)	23.3±13.5	28.6±10.8	0.038
AugP (mmHg)	7.2±6.6	8.7±5.3	0.250
CSBP (mmHg)	115.8±20.3	117.5±18.5	0.682
CDBP (mmHg)	85.0±15.4	85.9±13.4	0.768
Antihypertensive usage (n, %)			
ACEI or ARB	19 (61.3)	33 (47.1)	0.189
CCB	10 (32.3)	34 (48.6)	0.127
Beta blocker	7 (22.6)	10 (14.3)	0.304
Thiazide diuretic	4 (12.9)	11 (15.7)	1.000
Alpha blocker	2 (6.5)	4 (5.7)	1.000

BMI: body mass index; eGFR: estimated glomerular filtration rate; ALP: alkaline phosphatase; PTH: parathyroid hormone; PWV: pulse wave velocity; Alx@75: augmentation index normalized with 75/min heart rate; AugP: augmentation pressure; CDBP: central diastolic blood pressure; CSBP: central systolic blood pressure; ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; CCB: calcium channel blocker.
Variable values were expressed as number (n, %), mean±SD, or median (25-75 percentile).

Mean Alx@75 value was significantly higher in group II (28.6±10.8% vs. 23.3±13.5%, p=0.038). The PWV values in group I and group II were 8.0±1.7 and 8.2±1.4 m/s, respectively, but the difference was not significant (Figure 2). Serum albumin (p<0.001), hemoglobin (p=0.005), calcium (p=0.041), and eGFR (p=0.041) were significantly lower in group II. Mean age, BMI, parathyroid hormone and uric acid were similar in both groups. Twenty four-hour proteinuria was significantly higher in group II. Group II had a significantly higher ratio of female patients; 82% of all the females in the study were in group II (p=0.006). Demographic features of the groups are shown in Table 1. There was a significant gender difference in mean 25(OH) D levels: 12.2±7.8 ng/mL among female patients and 16.0±7.7 ng/mL for male patients (p=0.016).

In an analysis of all patients, 25(OH)D level was inversely correlated with Alx@75 (p=0.002, r=-0.307), augmentation pressure (p=0.030, r=-0.216), parathyroid hormone (p=0.014, r=-0.255), proteinuria (p=0.018, r=-0.252) and BMI (p=0.042, r=-0.203), while 25(OH)D level positively correlated with albumin (p<0.001, r=0.394), hemoglobin (p=0.031, r=0.215), eGFR (p=0.016, r=0.239), calcium (p=0.014, r=0.243) and transferrin (p=0.040, r=0.344). To identify independent determinants of 25(OH)D, a multivariate regression analysis was performed on the parameters that were found to be correlated with 25(OH)D. In backward multiple regression analysis, 25(OH)D was independently associated with Alx@75 (beta=-0.469, p=0.001) and albumin (beta=0.447, p=0.002).

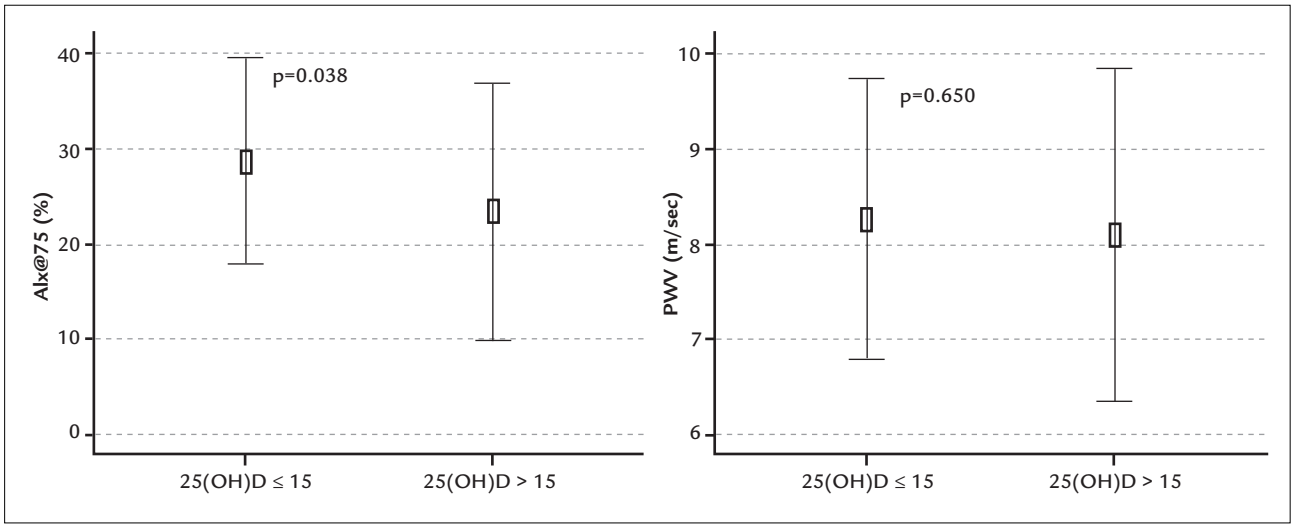

FIGURE 2 Augmentation index and pulse wave velocity values of the groups.
[Alx@75 and PWV; mean±standard deviation]

Discussion

Vitamin D deficiency is a worldwide problem. Studies conducted with healthy subjects found 25(OH)D deficiency at rates of 42% in America,[19] 40.4% in Europe[20] and 60% in Eastern countries.[21] A meta-analysis showed that 88% of healthy individuals have 25(OH)D lower than 30 ng/mL.[22] The prevalence of vitamin D deficiency in CKD patients not on dialysis has been reported between 21.5-58.3%,[15,23-25] and mean 25(OH)D was determined as 18±8 ng/mL.[15] In the present study, the prevalence of vitamin D deficiency was 69.4%; only 5.9% of patients had 25(OH)D levels higher than 30 ng/mL, and mean 25(OH)D was 14.1±7.9 ng/mL. Vitamin D deficiency is common in CKD, which has been attributed to many factors such as reduced sun exposure, decreased vitamin D-binding protein, proteinuria, reduced dietary intake, advanced age, malabsorption, and down-regulation of megalin levels.[8,15,26,27]

In Middle Eastern and South Asian developing countries, levels of 25(OH)D < 10 ng/mL were reported in 50% of the population and higher risk was noted among females.[28] Of females aged 24-77 years living in Rabat, 91% had lower than 30 ng/mL 25(OH)D, and female sex was considered a predictor of 25(OH)D deficiency.[29] Reports of 25(OH)D deficiency in females tend to be particularly common in the Asia/Pacific and Middle East/Africa regions, possibly due to women wearing a more covered clothing style compared to females in other parts of the world.[22] Vitamin D deficiency in females was significantly higher in our study, in accordance with previous studies.[23,28] This may be attributable to the covered clothing style worn by Turkish females due to cultural factors.

It has been shown that PWV and Alx are negatively associated with 25(OH)D in healthy subjects, postmenopausal women, and patients with diabetes mellitus, peripheral arterial disease, rheumatologic diseases and kidney disease.[13-16,30,31] Brachial-ankle PWV was found to be significantly lower in CKD patients with 25(OH)D deficiency.[15]

It has been reported that flow-mediated dilatation as a marker of endothelial function was lower in vitamin D deficiency in patients with CKD, and improved with replacement of 25(OH)D. In addition, vitamin D supplementation significantly reduced biomarkers of endothelial dysfunction such as intracellular adhesion molecule (ICAM), vascular adhesion molecule (VCAM), endothelial leukocyte adhesion molecule (E-Selectin) and von Willebrand factor (vWF). It was concluded that vitamin D supplementation recovers vascular endothelial function.[32]

Cholecalciferol supplementation of 40,000 IU every week for 8 weeks had no significant impact on both PWV and Alx@75 in CKD patients as previously shown.[33] In another study, Chitalia et al.[32] administered two doses of 300,000 IU cholecalciferol at baseline and 8-weeks to CKD stage 3-4 patients, PWV decreased from 7.9±1.9 to 7.7±2.2 m/s and Alx decreased from 22±16% to 18±20% at week 16. However, they concluded that PWV and Alx tended to improve but did not reach statistical significance.

In our study, Alx@75, a marker of arterial stiffness, was higher among patients with 25(OH)D deficiency. An inverse relation between 25(OH)D level and Alx@75 was determined, and serum 25(OH)D was independently associated with Alx@75 in patients with CKD. These results may indicate that vitamin D deficiency contributes to the development

of arterial stiffness in CKD. Vitamin D has a beneficial impact on the renin-angiotensin system, endothelium mediated vasodilatation, insulin resistance, inhibition of vascular smooth muscle proliferation, macrophage activation and cytokine production.[10,12,34] Vascular smooth muscle cell proliferation, the renin-angiotensin-aldosterone system and macrophage invasion of blood vessel walls are activated by vitamin D deficiency. In addition, parathyroid hormone secretion and inflammatory cytokine gene expression are increased. All these pathological processes result in decreased vascular compliance, increased vascular calcification and inflammation, which may contribute to the development of arterial stiffnesss.[3,15,16,27]

Vitamin D deficiency is associated with cardiovascular disease, all-cause mortality, morbidity, poor clinical outcomes and rapid decline of eGFR in patients with CKD.[25,34,35]

Our study has some limitations. First, 25(OH)D tended to decrease as PWV and CKD stage increased. However, we were unable to definitively confirm the association of 25(OH)D deficiency with PWV and CKD stage due to a relatively small cohort. Secondly, this was a cross-sectional case-control study; therefore, we could not evaluate the effect of vitamin D treatment on arterial stiffness, CKD progression or mortality.

Conclusion

Our study demonstrates that there is a high prevalence of 25(OH)D deficiency and insufficiency in CKD patients, and 25(OH)D values were lower in female patients in particular. The Alx@75 marker of arterial stiffness was higher with 25(OH)D deficiency and negatively correlated with 25(OH)D. Our results revealed that serum 25(OH)D was independently associated with Alx@75. Consequently, 25(OH)D deficiency may be a contributing factor in the development of arterial stiffness in CKD.

Conflict of interest

The authors declare no conflict of interest.

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