Relationship between Vitamin D Deficiency, Albuminuria, Peripheral Artery Disease and 5-year Mortality in Chronic Kidney Disease

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ABSTRACT
Objective: To investigate the effects of vitamin D deficiency, albuminuria and peripheral artery disease (PAD) relationships, on 5-year mortality in patients with chronic kidney disease (CKD).

Methodology: Observational study.

Place and Duration of Study: Department of Internal Medicine, Kartal Dr Lutfi Kirdar City Hospital, İstanbul, Turkey, from August 2015 to August 2020.

Methodology: The study included patients with stage 2-4 CKD, who were not previously diagnosed with peripheral artery disease (PAD) and were not on hemodialysis. Each patient's ankle-brachial index (ABI) was measured at rest with a portable vascular hand doppler; and an ABI of <0.9 was considered to be PAD. The mortality status of the participants were confirmed by the national death reporting system.

Results: A total of 110 CKD patients, mean age of 62.1±9.7 years, 36.4% women, were included in the study. It was found that 17.3% of the patients had vitamin D deficiency, 15.4% had vitamin D insufficiency, 32.7% had asymptomatic PAD, 33.9% had microalbuminuria and 39.4% had macroalbuminuria. It was observed that as vitamin D levels decreased, the frequency of albuminuria, and the prevalence of PAD, was on an increasing trend. A significant correlation was found between 5-year mortality, gender, body mass index (BMI), glomerular filtration rate (eGFR), urine albumin creatinine ratio (UACR), hemoglobin A1c (A1c), calcium (Ca), phosphate (P), vitamin D, ankle brachial index (ABI), and the neutrophil lymphocyte ratio (NLR) as a result of univariate cox-regression analysis. In the multivariate cox-regression model, it was observed that vitamin D, ABI and UACR levels continued being significant, independent of age, gender, BMI and eGFR levels.

Conclusion: Vitamin D deficiency, PAD and albuminuria, which are separate predictors of mortality, were shown to be independent predictors of long-term mortality in CKD patients.

Key Words: Chronic kidney disease, Mortality, Peripheral arterial disease, Vitamin D deficiency, Albuminuria, Ankle-brachial index.

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INTRODUCTION
Vitamin D is an essential nutrient and hormone that has important roles primarily in the regulation of mineral levels, bone health, the immune function, cell proliferation, differentiation, and apoptosis. Vitamin D deficiency or insufficiency is common in the general population, especially in patients with chronic kidney disease (CKD). Peripheral artery disease (PAD) is the general term for atherosclerotic vascular constrictions or obstructions, which manifest itself with claudication in the legs when symptomatic, and with resting pain, ulceration, and gangrene that often occurs silently without being noticed; even leading to amputations in severe cases.

It is thought to affect 13% of people over the age of 50, 5% of whom are symptomatic. PAD, which poses a higher risk for cardiovascular disease and stroke, is associated with increased morbidity and mortality in CKD patients with factors such as a result of chronic inflammation, hypoalbuminemia, and a procalcific state.

eGFR and the urinary albumin creatinine ratio (UACR), which provides a quantitative basis for identification, staging and risk assessment of CKD, are also independent predictors of all-cause mortality and cardiovascular mortality in the general population.

It was observed that vitamin D deficiency, albuminuria and PAD have been separately associated with increased morbidity and mortality in various patient populations. Accordingly, this study aims to evaluate them together in CKD patients and to investigate their relationship with 5-year mortality.

METHODOLOGY
This study, designed as a prospective-observational study, compatible with the Helsinki Declaration, was conducted on CKD patients who were monitored from Department of Internal Medicine, Kartal Dr Lutfi Kirdar City Hospital, İstanbul, Turkey,
RESULTS

A total of 110 CKD patients with a mean age of 62.1 ± 9.7 years, of whom 40 (36.4%) were women, were included at the pre-dialysis stage in the study. It was determined that 7 (6.4%) patients smoked, 1 (0.9%) used alcohol, 29 (26.4%) were in the low-income group and 19 (17.3%) were in the high-income group. Sixty-three (57.3%) patients were found to have diabetes mellitus (DM), 101 (91.8%) hypertension (HT), 51 (46.4%) hyperlipidemia (HL), and 32 (29.1%) coronary heart disease (CHD).

Five (4.5%) of the patients were at stage 2, 28.2% (n: 31) at stage 3a, 42.7% (n: 47) at stage 3b and 24.5% (n: 27) at stage 4 CKD. The mean UACR of the patients was 343.9 ± 414.6 mg/g, while 29 (26.6%) of the patients were normoalbuminuric, 37 (33.9%) microalbuminuric and 43 (39.4%) were macroalbuminuric. However, the mean ABI of the patients was found to be 0.99 ± 0.23; 32.7% (36/110) of the patients had low ABIs and therefore PAD.

The average vitamin D of the entire patient population was 28.3 ± 15 μg/L, and as shown in Table I, it was determined that 67.3% of patients had a sufficient level of vitamin D, while 17.3% (19/110) of patients had vitamin D deficiency and 15.4% (17/110) had vitamin D insufficiency. Vitamin D levels in men were found to be more adequate than in women (mean of 25OH D3 in men 32 ± 14.6 μg/L vs. 21.5 ± 13.3 μg/L in women; p:<0.001). The frequency of DM was 44.6% in those with sufficient vitamin D, 73.7% in those with deficiency, and 94.1% in those with insufficiency. Parallel to this, the mean A1c levels also increased significantly (A1c 6.56 ± 1.4 %, 6.95b ± 1.6 %, and 8.59 ± 2.0 %, respectively).

Hyperparathyroidism was detected in 43.2% of those with sufficient vitamin D, 68.4% of those with deficiency, and 66.7% of those with insufficiency. Those with sufficient vitamin D had a UACR median of 94, those with insufficient vitamin D had a median of 332.7, and those with deficient vitamin D had a median 626.7, which differed significantly from each other (Table I).

While the frequency of PAD was found to be 28.4% in CKD patients who had sufficient vitamin D levels, 42.1% had an insufficiency and 41.2% had a deficiency [Y1].

The frequency of albuminuria was 50 (68.5%) in patients who had sufficient vitamin D levels, the prevalence was 15 (78.9%) in those with insufficiency, 15 (88.2%) in those with deficiency. It was also found that the frequency of albuminuria increased as the vitamin level decreased [Y2].

When the frequency of PAD was examined according to UACR levels, it was found to be 7 (24.1%) in normoalbuminuric, 11 (29.7%) in microalbuminuric, and 17 (39.5%) in macroalbuminuric patients [Y3]. ABI decreased the urinary albumin excretion increased.

It was determined that 15 of the 110 patients participating in this study died during the 5-year follow-up (mortality rate: 13.6%). It was found that the vitamin D levels of those who progressed to mortality were lower than those who survived (an average of 30.1±14.5 and 18.3 ±13.7 g/ml respectively).
Among all patients, 5 (6.8%) of those with sufficient vitamin D, 4 (21.1%) of those with insufficient vitamin D and 6 (35.3%) of those with deficient vitamin D died within 5 years. It was determined that the average height of the patients was lower, their SBP averages were higher, their ABI averages were lower, their PAD frequency averages were higher, and their duration of DM and HL was longer. It was found that A1c, neutrophil, potassium and phosphorus levels of the deceased patients were higher; their vitamin D and eGFR averages were lower; and their proteinuria and albuminuria levels were higher than those still alive (Table II).

As seen in Table III, a significant relationship was found between 5-year mortality with gender, BMI, eGFR, UACR, A1c, Ca*P, vitamin D, ABI and NLR as a result of the univariate cox-regression analyses.

As shown in Table III, age, gender, the relationship between vitamin D, ABI and UACR, and 5-year mortality was shown in the multivariate cox-regression model based on BMI and eGFR levels independently of each other [AHR:0.95 (0.91-1), p=0.033, respectively; AHR: 0.028 (0.001-0.62), p=0.024; AHR: 1.001 (1.00-1.00) p=0.018].

**DISCUSSION**

In this 5-year observational study, vitamin D, ABI, and albuminuria levels were found to be strong and independent predictors of all-cause deaths in CKD. These relationships were not only independent of each other but also independent of age, gender, BMI and glomerular filtration rate.
Table II: Clinical features of patients according to 5-year mortality.

<table>
<thead>
<tr>
<th>Clinical parameters</th>
<th>Survivors (n:95)</th>
<th>Non-survivors (n:15)</th>
<th>p-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Years)</td>
<td>61.7 (9.6)</td>
<td>64.2 (10.2)</td>
<td>0.365</td>
</tr>
<tr>
<td>Gender (Female)</td>
<td>65 (68.4%)</td>
<td>5 (33.3%)</td>
<td>0.009</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>81.9 (12.9)</td>
<td>83.1 (14.2)</td>
<td>0.751</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>166.3 (9.1)</td>
<td>161.1 (10.7)</td>
<td>0.046</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>29.7 (4.5)</td>
<td>32.2 (5.9)</td>
<td>0.058</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>105.6 (10.3)</td>
<td>111.1 (12.3)</td>
<td>0.062</td>
</tr>
<tr>
<td>Socioeconomic status (Low income)</td>
<td>25 (26.3%)</td>
<td>4 (26.7%)</td>
<td>0.482</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>140.0 (21.5)</td>
<td>157.3 (20.9)</td>
<td>0.004</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>80.7 (11.6)</td>
<td>82.0 (13.7)</td>
<td>0.703</td>
</tr>
<tr>
<td>Heart rate (per minute)</td>
<td>77.4 (9.8)</td>
<td>79.2 (6.8)</td>
<td>0.497</td>
</tr>
<tr>
<td>ABI</td>
<td>1.02 (.2)</td>
<td>.84 (.1)</td>
<td>0.005</td>
</tr>
</tbody>
</table>

Comorbidities

| PAD (%)                              | 26 (27.4%)       | 10 (66.7%)           | 0.003    |
| Chronic renal disease time (years)   | 3.6 (4.1)        | 3.4 (2.8)            | 0.871    |
| Diabetes mellitus (%)                | 51 (53.7%)       | 12 (80.0%)           | 0.056    |
| Hypertension (%)                     | 86 (90.5%)       | 15 (100.0%)          | <0.001   |
| Hyperlipidemia (%)                   | 42 (44.2%)       | 9 (60.0%)            | 0.254    |
| Coronary heart disease (%)           | 25 (26.3%)       | 7 (46.7%)            | 0.098    |
| Laboratory findings                  |                  |                      |          |
| Hemoglobin (g/dl)                    | 13.2 (1.6)       | 12.4 (1.7)           | 0.097    |
| Leukocyte (/μl)                      | 7810 (1848.0)    | 8520 (1556.6)        | 0.150    |
| Neutrophil (/mm3)                    | 4835 (1377.4)    | 5611 (1533.2)        | 0.044    |
| Lymphocyte (/mm3)                    | 2228 (780.4)     | 2081 (664.7)         | 0.530    |
| Platelet (/mm3)                      | 223044 (51110.8) | 236667 (60234.9)     | 0.367    |
| Hemoglobin A1c (%)                   | 6.6 (1.3)        | 8.9 (2.2)            | <0.001   |
| Urea (mg/dl)                         | 63.8 (23.9)      | 75.9 (31.9)          | 0.087    |
| Creatinine (mg/dl)                   | 1.8 (.5)         | 1.6 (.4)             | 0.229    |
| Sodium (mEq/L)                       | 138.4 (2.5)      | 138.4 (4.6)          | 0.968    |
| Potassium (mEq/L)                    | 4.7 (.5)         | 5.3 (1.1)            | 0.001    |
| Calcium (mg/dl)                      | 9.6 (.7)         | 9.3 (1.7)            | 0.142    |
| Phosphorus (mg/dl)                   | 3.4 (.6)         | 3.9 (.7)             | 0.011    |
| Parathyroid hormone (pg/ml)          | 99.0 (69.1)      | 96.6 (49.5)          | 0.934    |
| 25 OH vitamin D (ng/mL)              | 30.1 (14.5)      | 18.3 (13.7)          | 0.005    |
| UACR (mg/g)                           | 105.7 [18.9-466.4] | 535.6 [172.1-1227.7] | <0.001   |
| eGFR (mL/min/1.73m²)                 | 37.4 (12.1)      | 44.7 (15.3)          | 0.039    |
| NLR                                  | 2.5 (1.2)        | 3.3 (2.5)            | 0.041    |
| Ca×P                                 | 32.9 (6.4)       | 35.1 (7.5)           | 0.232    |

Data are means (SD), number (%), or medians [interquartile range]. NLR: Neutrophil/Lymphocyte ratio. UACR: urinary albumin creatinine ratio. eGFR: estimated glomerular filtration rate by CKD-epi. ABI: ankle-brachial index.

According to National Health and Nutrition Examination Survey (NHANES) data, it was found that low 25 (OH) D levels were strongly associated with a high prevalence of PAD (across quartiles of 25(OH)D, from lowest to highest, the prevalence of PAD was 8.1%, 5.4%, 4.9%, and 3.7%); and with increased albuminuria (a stepwise increase in the prevalence of albuminuria was observed with decreasing quartiles of vitamin D concentration: 8.9%, 11.5%, 13.7%, and 15.8%). Since the population of this study consisted of CKD patients, a much higher PAD prevalence (32.7%), and therefore higher rates of albuminuria (73.4%), was detected. However, similar to other studies it was shown in this study that the prevalence of PAD and the incidence of albuminuria increased as the vitamin level decreased.

In a study by Van de Luijtgaarden et al., low vitamin D levels were found to be associated with increased carotid-intima-media thickness and lower ABI independent of cardiovascular risk factors. Similarly, in this study, low vitamin D levels were associated with low ABI levels.
Table III: Crude HRs and adjusted HRs for predictors of 5-years mortality.

<table>
<thead>
<tr>
<th></th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sig.</td>
<td>HR</td>
</tr>
<tr>
<td>Age</td>
<td>0.367</td>
<td>1.025</td>
</tr>
<tr>
<td>Gender, female</td>
<td>0.015</td>
<td>0.265</td>
</tr>
<tr>
<td>BMI</td>
<td>0.047</td>
<td>1.118</td>
</tr>
<tr>
<td>Socioeconomic status</td>
<td>0.514</td>
<td>0.772</td>
</tr>
<tr>
<td>Marital status</td>
<td>0.415</td>
<td>1.609</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0.077</td>
<td>0.320</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.435</td>
<td>0.043</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>0.246</td>
<td>1.842</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>0.119</td>
<td>2.242</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.224</td>
<td>0.447</td>
</tr>
<tr>
<td>Urea</td>
<td>0.060</td>
<td>1.018</td>
</tr>
<tr>
<td>eGFR</td>
<td>0.032</td>
<td>1.042</td>
</tr>
<tr>
<td>UACR</td>
<td>0.000</td>
<td>1.002</td>
</tr>
<tr>
<td>Hemoglobin A1c</td>
<td>0.000</td>
<td>1.788</td>
</tr>
<tr>
<td>Calcium</td>
<td>0.044</td>
<td>0.673</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>0.008</td>
<td>2.848</td>
</tr>
<tr>
<td>Parathyroid hormone</td>
<td>0.920</td>
<td>1.000</td>
</tr>
<tr>
<td>25 OH vitamin D</td>
<td>0.005</td>
<td>0.939</td>
</tr>
<tr>
<td>ABI</td>
<td>0.007</td>
<td>0.047</td>
</tr>
<tr>
<td>NLR</td>
<td>0.010</td>
<td>1.490</td>
</tr>
<tr>
<td>Ca*P</td>
<td>0.222</td>
<td>1.050</td>
</tr>
</tbody>
</table>


While those with sufficient vitamin D had a low ABI rate of 28.4%, those with low vitamin D had a low ABI rate of 41.7%.7

The exact mechanisms of action behind the increased prevalence of asymptomatic PAD due to vitamin D deficiency are unclear. Vitamin D plays a role in the regulation of calcium homeostasis in the body. The positive effects of vitamin D on cardiovascular health have been shown by various studies. Available data indicate that not only vitamin D excess but also vitamin D deficiency shows a biphasic 'dose-response' curve on vascular calcification.8,9 Recent genetic studies have shown that even in the presence of an extremely high serum of 1,25-dihydroxy vitamin D and calcium levels, vascular calcification can be prevented by lowering serum phosphate levels.10,11 Vitamin D levels were also found to be associated with suppression of the renin-angiotensin-aldosterone system,12 atheroprotective effects,13 renal anti-inflammatory effects,14 and immunomodulatory effects.8,15

In a study conducted on CKD patients, it was shown that there is a strong relationship (a 54% increase in risk) between 25 (OH) D deficiency and albuminuria, independent of GFR levels.16 Similarly in this study, it was shown that both microalbuminuria and macroalbuminuria rates were on an increasing trend as vitamin D deficiency deepened. In the relationship between vitamin D deficiency and albuminuria, the improvement in albuminuria observed with active vitamin D treatment in patients with CKD17 can be presented as evidence, and it is thought that the increased filtration of albumin into the urinary cavity prevents vitamin D reabsorption, thus contributing to greater loss of vitamin D in the urine.18

The relationship between albuminuria and cardiovascular disease (CVD) is increasingly recognised, but its relation to PAD is not clear. It was found in a study by Borch-Johnsen et al. that albuminuric diabetic subjects with or without hypertension had a six-fold higher risk of PAD than those without albuminuria.19 Similarly, Wattanakit et al. determined that the presence of albuminuria, regardless of its level, was an important risk factor for PAD in diabetic patients, but did not find a similar relationship in non-diabetic patients.20 In another study, it was emphasised that the amount of albuminuria was also important, showing that the prevalence of foot ulcers in diabetic patients increased as urinary excretion of albumin increased.21 However, the situation is somewhat contradictory in non-diabetics. Yudkin et al. demonstrated that the prevalence of PAD increased six times in subjects with microalbuminuria compared to those without albuminuria. However, the Cardiovascular Heart Study, a large population-based study, showed that albuminuria was not an inde-
If the pathophysiological mechanisms of the albuminuria-PAD relationship are considered, the strongest hypothesis is that albuminuria is an indicator of endothelial dysfunction. As evidence of this, it is thought that hyperglycemia in diabetic individuals triggers the formation of oxidative stress in endothelial cells with advanced glycation end-products, accelerates atherosclerosis with vascular smooth muscle cell proliferation, thus leading to PAD. In a different study by Joergensen et al., the relationship between low vitamin D levels and asymptomatic CAD was found in type 2 DM patients with increased UACR. In this study, it was also determined the effects of low levels of ABI, which is an asymptomatic PAD marker, UACR and vitamin D on mortality.

In the literature on mortality, each of the parameters studied here, was shown to be associated with mortality separately. Joergensen et al. showed that vitamin D deficiency increased mortality independently of UACR. Kunihiro et al. reported that albuminuria increased all-cause mortality even in the general population.

This current study on the other hand, is valuable in terms of evaluating these variables, each of which is a separate predictive factor, and showing the level of relationship with mortality, deeming it worthy of presentation.

Besides its strengths, this study of course has some limitations. The sample size of this study was limited and cannot be generalised to the whole population since it was conducted on a special patient group, such as CKD. More extensive prospective observational studies that can contribute to the understanding of the relationships detected and support the findings are needed in the future.

CONCLUSION
In this 5-year observational study, vitamin D, ABI, and albuminuria levels were found to be strong and independent predictors of all-cause deaths in CKD. These relationships were not only independent of each other but also independent of age, gender, BMI and glomerular filtration rate.

ACKNOWLEDGEMENT:
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ETHICAL APPROVAL:
Ethical approval was obtained prior to initiation of the research work from Kartal Dr Lutfi Kirdar City Hospital Ethics Committee (89513307/1009/430-26/03/2015).

PATIENTS' CONSENT:
Informed consents were obtained from each patient to publish the data.

CONFLICT OF INTEREST:
The author declared no conflict of interest.

AUTHOR’S CONTRIBUTION:
There is only one author who meets all criteria for authorship according to ICJME.

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