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The prevalence of peripheral artery disease in older adults with chronic kidney disease

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ABSTRACT

Aims: Not only severe but also mild to moderate chronic kidney disease (CKD) is an independent risk factor for peripheral artery disease (PAD). In this study, we examined the prevalence of PAD among older adults with mild-to-moderate CKD.

Methods: The study was performed using the dataset of participants registered to a previous single-center, cross-sectional study that included non-institutionalized older adults aged 65 years or older in a geriatric outpatient setting. The subjects were patients with mild to moderate CKD. Ankle brachial index (ABI) was measured using a hand-held Doppler. PAD was diagnosed using an ABI value <0.9. The crude and adjusted prevalence of PAD were calculated.

Results: A total of 554 patients were included (age: 75.4±6.2 years; female: 67.3%). PAD was detected by 8.2%, 27.1%, 60.0%, and 4.7%, in stage 1, 2, 3 and 4 CKD, respectively, with significant difference in stage 2 (p=0.003) and stage 3 (p=0.011) CKD compared with the stage 1 disease. PAD was also more prevalent in patients with reduced estimated glomerular filtration rate (eGFR) (<60 mL/min/1.73 m^2 vs. ≥60 mL/min/1.73 m^2: 19.6% vs. 10.9%, p=0.005). However, after adjustment for potential confounders, the increase in the prevalence of PAD in subjects with lower eGFR was no longer significant (Odds ratio: 1.48, 95% confidence interval: 0.87-2.53, p=0.148).

Conclusions: This study showed a higher prevalence of PAD among older adults with mild-to-moderate CKD; however, the difference appears to depend on existing confounders.

Introduction

The occlusive atherosclerotic disease of the aorta and lower extremities are known as peripheral artery disease (PAD). PAD is classified as an atherosclerotic cardiovascular disease (ASCVD) with coronary artery disease (acute coronary syndrome, history of myocardial infarction, stable or unstable angina or coronary or other arterial revascularization), stroke, and transient ischemic attack (1-3).

The prevalence of PAD in the general population is around 3-10% (4,5). Also, independent of cardiovascular disease (CVD) risk factors, the incidence of the PAD progresses with age and reaches 15-20% in patients aged 70 years or older (4,5). In the CAREFUL study, the first multicenter national study that investigated the prevalence of PAD in Turkey, subjects aged 70 years or older, or subjects aged 50-69 years with at least one cardiovascular risk factor were enrolled (6). The results of the study demonstrated that the prevalence of PAD was 20% in the study population, and 30% in patients aged 70 years or older (6). PAD accompanies complex chronic diseases of older age, as was shown in different types of dementia (7).

Although the gold-standard test for the diagnosis of PAD is conventional or computed tomography angiography, the ankle-brachial index (ABI) measurement, a non-invasive, simpler, efficient, and cheaper diagnostic tool, became a preferable option in the diagnosis of PAD with sensitivity (Sen) and specificity (Spe) above 90% in all age groups (8,9). Another alternative non-invasive technique used in the diagnosis of PAD is the arterial Doppler ultrasonography of the lower extremities (10). However, its preference is limited due to its poor performance in the diagnosis of infrapopliteal disease, inter-observer variability of the technique, and higher costs (10). Pulse wave velocity measurement, a non-invasive tool for the assessment of arterial stiffness, and Edinburgh Claudication Questionnaire, a screening tool for the detection of intermittent claudication were also studied as alternative methods for ABI, but results revealed that these tools cannot be used instead of each other (11,12).

Chronic kidney disease (CKD) is prevalent among older adults and is associated with increased morbidity and mortality (13). Most older adults have a mild to moderate decrease in estimated glomerular filtration rate (eGFR) and a higher frequency of CKD due to the comorbidities (14). The overall prevalence of CKD in the general population is around 11%, reaching greater than 40% after the 6th decade (15).

Mild-to-moderate CKD is associated with a higher risk of ASCVD (16), which is more pronounced for older adults (17). However, most studies have focused on coronary artery disease (16). Only a few studies have been published on the association of PAD in patients with renal insufficiency (18). Thus, current knowledge on the frequency of PAD among older adults with CKD is considered limited. In this study, we investigated the prevalence of lower extremity PAD in older adults with mild-to-moderate CKD.

Methods

Study population

This study was performed using the dataset of participants registered to a previous single-center, cross-sectional study that included non-institutionalized older adults aged 65 years or older in a geriatric outpatient setting (19). Subjects receiving renal replacement therapy, having a history of lower extremity revascularization, recent major surgery, or extremity amputation, severely impaired in daily activities, residing in a nursing home, wheelchair bounded, or considered to have a short life expectancy due to malignancies or any other medical conditions and those who declined to participate were excluded from the original cohort. For the current analysis, subjects diagnosed with dementia were further excluded.

The institutional review board approved the study, and the participants provided written, informed consent when enrolled to the original study. The study protocol conforms to the Helsinki Declaration of 1975, as revised in 1983.

Working protocol

The basic characteristics of the subjects including age, gender, and self-reported education attained in years, current or past smoking status, and comorbidities including diabetes mellitus, hypertension, hypercholesterolemia, cardiovascular disease (CVD), coronary heart disease, stroke, anemia, hypothyroidism, vitamin B12 deficiency, and folate deficiency, body mass index (BMI), and laboratory results were available in the registry dataset.

Calculation of GFR and determination of CKD stages

Serum creatinine level was used to calculate eGFR (mL/min/1.73 m^2) by using the Modification of Diet in Renal Disease (MDRD) study equation to determine the degree of kidney impairment (20). Stages of CKD was defined according to the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline as follows: stage 1 CKD: GFR ≥90 mL/min/1.73 m^2; stage 2 CKD: GFR 60 to 89 mL/min/1.73 m^2; stage 3 CKD: GFR 30 to 59 mL/min/1.73 m^2; stage 4 CKD: GFR 15 to 29 mL/min/1.73 m^2; stage 5 CKD: GFR <15 mL/min/1.73 m^2 or treatment by dialysis. However, individuals with CKD stage 5 (n=2) were not included due to the very low number of subjects in the analyses because they were excluded from the original study.

Measurement of ABI

ABI was measured in an improved facility by the conventional method as previously described (7,21-23). Briefly, patients were placed on a stretcher in the supine position with both arms slightly open. Two metal armrests of 30 cm width and 90 cm length were placed to the stretcher with an angle of 30º degrees to support both arms. In addition, sponge rubbers were placed under the heels and elbows to slightly elevate the extremities from the surface below the heart level to allowing the operator to place the cuff ideally. Four fully calibrated and identical aneroid sphygmomanometers with Velcro cuffs (ERKA, D-83646, Bad Tölz, Germany) of 12 cm width and 29 to 42 cm length were wrapped on four extremities at the same time. After resting at least for five minutes in supine, measurements were performed using a handheld 8-MHz Doppler instrument (Hadeco, Kawasaki, Japan). The measurements were started from the right upper arm and followed by the right ankle left ankle and left upper arm. This cycle was performed twice. The first sound of blood flow heard during the deflation of the cuff for both brachial pulses in the upper arms and dorsalis pedis and tibialis posterior pulses in both ankles were recorded. The mean value of the two measurements was recorded as the result for the respective vessel.

Calculation and interpretation of ABI results

The ABI was calculated based on the Trans-Atlantic Inter-Society Consensus Document on Management of Peripheral Arterial Disease (TASC II) guidelines (9). The right and left ABIs were calculated separately by dividing the highest systolic blood pressures of each lower extremities (a. dorsalis pedis or a. tibialis posterior) to the systolic blood pressure of the brachial artery on the same side. Finally, the lower ABI value on the left or right side was recorded as the final ABI value. Individuals who had an ABI value of 0.9 or lower were diagnosed with PAD. Besides, subjects with an ABI value greater than 1.40 (n=3) were excluded as it indicates noncompressible arteries that interfere with the correct assessment of the ABI.

Statistical Analysis

Results are displayed as the mean and standard deviation for normally distributed continuous variables. The normality of distribution was tested using the Shapiro-Wilk test. Categorical data are displayed as absolute numbers and a percentage of the total. The differences between the continuous variables were tested by the t-test. The chi-square test was used to compare the categorical variables. The Sen and Spe analysis was conducted to determine the effects of different stages of CKD on PAD. The study sample was divided into 3 tertiles according to the eGFR, as follows; tertile 1: eGFR <49.4 mL/min/1.73 m^2 (n=138, 25 percentile), tertile 2: eGFR between 49.5-72.2 mL/min/1.73 m^2 (n=277, 50 percentile), tertile 3: eGFR >72.3 mL/min/1.73 m^2 (n=139, 75 percentile). Tertile 1 had the lowest and tertile 3 had the highest eGFR. The analysis of continuous variables across tertiles was performed using one-way ANOVA or the Kruskal-Wallis test, and the analysis of categorical variables was performed using the chi-square test. Multivariable logistic regression analysis was used to test the independent association between the eGFR and PAD. The Hosmer-Lemeshow test was used to evaluate the goodness of fit of the model. Statistical significance was set at p value <0.05. Statistical Package for the Social Sciences for Windows, version 26.0, IBM. Corp., Armonk, NY, 2019 was used for statistical analysis for all data.

Results

Study population

The study included 554 older adults (mean age: 75.4±6.2 years, women: 67.3%). Women were significantly younger than men (mean age: 74.8±6.3 vs. 76.8±5.8; p<0.001). Basic demographics and clinical characteristics are given in Table 1. The mean eGFR was 62.0±20.6 mL/min/1.73 m^2, and men have lower mean value than woman (59.5±17.2 mL/min/1.73 m^2 vs. 63.2±22.0 mL/min/1.73 m^2; p=0.032).

Frequency of PAD according to the stages of CKD and tertiles

In the whole study group, the frequency of patients with a 0.9 or lower ABI was 15.3% (n=85). The prevalence of PAD among

Table 1. Basic characteristics of the subjects

	Total (n=554)	Female (n=373, 67.3%)	Male (n=181, 32.7%)	p
Age, mean (SD)	75.4 (6.2)	74.8 (6.3)	76.8 (5.8)	**<0.001**
65-74, n (%)	277 (50.0)	203 (36.6)	74 (13.4)	**0.001**
75-84, n (%)	231 (41.7)	143 (25.8)	88 (15.9)	**0.041**
>84, n (%)	46 (8.3)	27 (4.9)	19 (3.4)	**0.029**
eGFR, mean (SD)	62.0 (20.6)	63.2 (22.0)	59.5 (17.2)	**0.032**
BMI, mean (SD)	29.8 (5.6)	30.8 (5.9)	27.7 (4.3)	**<0.001**
Lower education, n (%)	390 (70.5)	316 (57.1)	74 (13.4)	**<0.001**
Past/current smoking, n (%)	152 (27.4)	40 (7.2)	112 (20.2)	**<0.001**
Diabetes mellitus, n (%)	146 (26.4)	107 (19.3)	39 (7.0)	0.074
Hypertension, n (%)	432 (78.0)	300 (54.2)	132 (23.8)	**0.046**
Hypercholesterolemia, n (%)	224 (40.4)	160 (28.9)	64 (11.6)	0.090
Anemia, n (%)	92 (16.6)	78 (14.0)	14 (2.6)	**0.007**
Hypothyroidism, n (%)	62 (11.5)	48 (8.9)	14 (2.6)	0.056
Vitamin B12 deficiency, n (%)	168 (30.3)	107 (19.3)	61 (11.0)	0.228
Folate deficiency, n (%)	62 (11.9)	35 (6.7)	27 (5.2)	0.085
CVD, composite, n (%)	138 (24.9)	66 (11.9)	72 (13.0)	**<0.001**
Coronary heart disease, n (%)	109 (19.7)	50 (9.0)	59 (10.6)	**<0.001**
Stroke, n (%)	36 (6.5)	19 (3.4)	17 (3.1)	0.054

Lower education: <5 years of attained education level, anemia: hemoglobin <12 g/dL in woman, and hemoglobin <13 g/dL in man, hypothyroidism: thyroid stimulating hormone >5 mIU/mL, vitamin B12 insufficiency: <200 pg/mL, folate deficiency: <5 ng/mL, CVD: Presence of either coronary heart disease or stroke. Significant p values are in bold. See text for other details.
SD: Standard deviation, eGFR: Estimated glomerular filtration rate, BMI: Body mass index, CVD: Cardiovascular disease

subjects with stage 1, 2, 3 and 4 CKD was given in Table 2. Stage 1 and stage 4 CKD groups showed similar proportion of PAD (8.2% vs. 7.9%, p=0.914, and 3.0% vs. 4.7%, p=0.410, respectively). The frequency of PAD was lower in stage 2 CKD (27.1% vs. 44.1%, p=0.003), and higher in stage 3 CKD (60.0% vs. 45.0%, p=0.011) (Table 2). Also, the prevalence of PAD was higher in patients with a reduced (<60 mL/min/1.73 m^2) vs. higher eGFR (19.6% vs. 10.9%, p=0.005). However, after adjustment for potential confounders (age, gender, smoking, diabetes mellitus), the increase in the prevalence of PAD in subjects with reduced eGFR was no longer significant [OR: 1.48, 95% confidence interval (CI): 0.87-2.53, p=0.148] (Hosmer-Lemeshow test, p=0.890).

The frequency of PAD between the eGFR tertiles was significantly different (tertile 1: 36.5%, tertile 2: 48.2%, and tertile 3: 15.3%, p=0.010) (Table 2). The comparison of patients in the lowest and highest tertiles showed that the mean ABI value was significantly higher (T1: 0.99±0.19 vs. T3: 1.07±0.14, p<0.001), and the prevalence of PAD was significantly lower (T1: 22.5% vs. T3: 9.4%, p=0.003) in the highest tertile (Table 3).

The Sen and Spe of each CKD stages and reduced eGFR to detect PAD were as follows; stage 1 CKD=8.2% Sen and 92.1% Spe; stage 2 CKD=27.1% Sen and 55.9% Spe; stage 3 CKD=60.0% Sen and 55.0% Spe; stage 4 CKD=4.7% Sen and 97.0% Spe, and eGFR <60 mL/min/1.73 m^2=64.7% Sen and 57.0% Spe.

Discussion

The results of this study showed that an eGFR value below <60 mL/min/1.73 m^2 is associated with a higher frequency of PAD among older patients. Also, the comparison of subjects in the lowest and highest eGFR tertiles showed that PAD was more prevalent, and the mean ABI value was lower in the lowest eGFR tertile. However, adjusted for age, gender, smoking status, and diabetes mellitus, the difference in the prevalence of PAD patients with eGFR below and above 60 mL/min/1.73 m^2 became saturated.

The risk of ASCVD associated ischemic events is higher in CKD patients than in individuals with preserved kidney function (24). The PAD, similar to other ASCVD, is also more frequent in CKD patients than in the general population (25). Although the association between severe CKD and PAD in the general population is well established (25), the data related to the association of mild to moderate CKD and PAD among older adults are limited. Most of the studies that focused on the association of ASCVD and reduced eGFR among older adults excluded patients with PAD (17,26). Either the rate of PAD patients in the study cohort was limited (27), or the participants were mostly younger than 65 years in other studies (18).

Table 2. Frequency of peripheral artery disease according to the stages of chronic kidney disease and tertiles

	Total (n=554)	Peripheral artery disease (n=85, 15.3%)	No peripheral artery disease (n=469, 84.7%)	p
Stage 1 CKD, n (%)	44 (7.9)	7 (8.2)	37 (7.9)	0.914
Stage 2 CKD, n (%)	230 (41.5)	23 (27.1)	207 (44.1)	**0.003**
Stage 3 CKD, n (%)	262 (47.3)	51 (60.0)	211 (45.0)	**0.011**
Stage 4 CKD, n (%)	18 (3.2)	4 (4.7)	14 (3.0)	0.410
eGFR tertiles, n (%)				
Tertile 1	138 (24.9)	31 (36.5)	107 (22.8)	
Tertile 2	277 (50)	41 (48.2)	236 (50.3)	**0.010**
Tertile 3	139 (25.1)	13 (15.3)	126 (26.9)	

Stage 1 CKD: eGFR ≥90 mL/min/1.73 m^2, stage 2 CKD: eGFR between 89-60 mL/min/1.73 m^2, stage 3 CKD: eGFR between 59-30 mL/min/1.73 m^2, stage 4 CKD: eGFR between 29-15 mL/min/1.73 m^2, tertile 1: eGFR <49.4 mL/min/1.73 m^2, tertile 2: eGFR between 49.5-72.2 mL/min/1.73 m^2, tertile 3: eGFR >72.3 mL/min/1.73 m^2. Significant p values are in bold.
CKD: Chronic kidney disease, eGFR: Estimated glomerular filtration rate

Table 3. Comparison of the frequency of peripheral artery disease and the mean ankle brachial index values in subjects with reduced and preserved estimated glomerular filtration rate and in lowest and highest tertiles

	Estimated glomerular filtration rate		
	Reduced (n=280)	Preserved (n=274)	p
PAD, n (%)	55 (19.6)	30 (10.9)	**0.005**
	Tertile 1 (n=138)	**Tertile 3 (n=139)**	
PAD, n (%)	31 (22.5)	13 (9.4)	**0.003**
ABI, mean (SD)	0.99 (0.19)	1.07 (0.14)	**<0.001**

Reduced eGFR: <60 mL/min/1.73 m^2, preserved eGFR: ≥60 mL/min/1.73 m^2, significant p values are in bold.
PAD: Peripheral arterial disease, eGFR: Estimated glomerular filtration rate, SD: Standard deviation, ABI: Ankle-brachial index

In a study conducted in Spain with 102 older adults with CKD, patients with reduced eGFR (<60 mL/min/1.73 m^2) were diagnosed with PAD by 32%, markedly higher than the prevalence of PAD in Spanish population without CKD (6.9%) (28). However, the authors performed only unadjusted analyses. Although we diagnosed more patients with PAD among CKD patients with a reduced eGFR (<60 mL/min/1.73 m^2) in crude comparisons, the difference was no longer significant in the adjusted analysis.

In a longitudinal study conducted with 4893 subjects aged 65 years or older, participants were followed up for a mean of 4.33 years to determine the relationship between baseline kidney function and the development of ASCVD (29). The authors identified that 25.1% (n=1229) of the participants were diagnosed with ASCVD during follow-up, but only 1.5% (n=18) were PAD. The authors also reported that each 10 mL/min/1.73 m^2 decline in eGFR was associated with an increased risk of ASCVD, including PAD. However, the number of PAD diagnoses in that study was limited. Also, the authors did not perform a subgroup analysis with PAD patients to investigate whether the increased risk of ASCVD due to a decrease in eGFR could have been similarly attributed to the PAD patients or not.

According to results of the National Health and Nutrition Examination Survey of 1999-2000, the prevalence of PAD among patients with an eGFR <60 mL/min/1.73 m^2 vs. higher was found 24% vs. 3.7%, respectively (25). Moreover, the association of PAD and CKD remained significant after adjustment for potential confounders, which contrasts with our results of frequency analysis as the difference in the prevalence of PAD among subjects with low vs. preserved eGFR was not significant controlling for potential covariates. The exclusion of patients with stage 5 CKD/renal replacement therapy and significantly older age of the study population in our study may explain the difference between the two studies (30,31).

In a prospective follow-up study by Wattanakit et al. (26), a total of 14280 participants with a mean age of 54 years were followed up for a mean of 13.1 years to investigate whether the level of kidney function was an independent risk factor for PAD. Age and gender-adjusted relative risk (RR) for PAD was 1.04 (95% CI: 0.91-1.18) for those with stage 1 and 2 CKD, and 1.82 (95% CI: 1.34-2.47) for those with stage 3 and 4 CKD. After adjustment for confounders of ASCVD development, although the RR was reduced, patients with CKD were still at an increased risk of incident PAD (RR of 1.56; CI: 1.13-2.14). The findings suggested an inverse correlation between the risk of PAD and kidney functions across all stages of CKD. We were unable confirm that finding among mild-to-moderate CKD patients in our study. On the explanation may be the unexpectedly high frequency of PAD in patients with preserved renal functions due to the advanced age of our cohort.

PAD is more frequent in CKD patients than in the general population (25). However, the causal relationship between CKD and PAD has not yet been fully elucidated. The prevailing opinion on this subject is that CKD is probably a marker of metabolic diseases leading to progressive dysfunction of vascular structure (32,33). This suggestion is mostly based on studies that have investigated the association of atherosclerosis and albuminuria that is a marker of endothelial dysfunction (34). The association between albuminuria, medial arterial calcification and PAD is well established (35,36). In addition to the direct impact of CKD on arteries, the risk factors for both CKD and PAD development are quite similar, though not identical (37,38). In the Chronic Renal Insufficiency Cohort study, novel risk factors associated with an increased prevalence of PAD in patients with CKD were oxidative stress, inflammation, insulin resistance, and a prothrombotic state (39).

This study has some limitations. First, this was a retrospective analysis of a dataset created to explore the association of ABI and bone mineral density (19). Therefore, the study may be underpowered to study the relationship between severely reduced kidney functions and ABI or peripheral arterial disease. Second, we calculated eGFR by using serum creatinine level at study entry using the MDRD study equation, which requires stable kidney function (39). Although the participants were community-dwelling outpatients, the current study did not specifically assess the course of kidney functions for at least three months. Third, it is well-known that the prevalence of PAD is significantly higher among dialysis patients (25) and end-stage CKD patients (36). However, we excluded stage 5 CKD patients and patients receiving renal replacement therapy, which might have caused a similar distribution of PAD between lower and higher eGFR groups after adjustment for confounders.

Conclusion

In conclusion, this study showed evidence of a higher prevalence of PAD in older people with CKD. However, the observed difference appeared to depend on existing confounders in multivariable regression analyses, suggesting that the risk of PAD in older adults with CKD is not modified independently from other risk factors for atherosclerotic diseases. Based on the findings in our study and current literature, future prospective studies with larger sample size must better identify the association of mild to moderate CKD with PAD among older adults.

Ethics

Ethics Committee Approval: The Kecioren Training and Research Hospital Institutional Review Board approved the study (approval number: 2012-KAEK-15/1256-2017, date: 11.01.2017).

Informed Consent: This study is an analysis of a data set from a prospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: İ.T., Design: İ.T., Data Collection or Processing: B.B.B., İ.T., Analysis or Interpretation: B.B.B., İ.T., Literature Search: B.B.B., İ.T., Writing: B.B.B., İ.T.

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