schemic Type of Diabetic Foot in Patients with and without Chronic Kidney Disease in Assiut University Hospitals: Case Control Study

Effat Abdelhady Tony[1], Walla A Khalifa[1], Mohamed Hasan Mohamed Abd Ellah Alawi[1], Abeer Abdelhady Tony[2], Usra Mohamed Farrag Ahmed[*2]

[1]Internal Medicine and Endocrinology, Internal Medicine Department, Assiut University Hospital, Assiut University, Egypt.

[2]Department of Neuropsychiatry, Faculty of Medicine, Aswan University, Aswan, Egypt.

[*]***Corresponding Author:*** Usra Mohamed Farrag Ahmed

E-mail: Usramohamed24@aun.edu.eg

Abstract:

Background*:* Despite the significance of these concerns, little is known about the potential relationship between chronic kidney disease and diabetic foot disease.

***Aim* and Objectives:** are to detect ischemic type of foot disease in both diabetic non-CKD patients and diabetic CKD patients, and to assess factors that aggravate ischemic type of foot abnormalities in diabetic CKD patients by measuring serum calcium, phosphorus, potassium, parathyroid hormone, albumin, uric acid, hemoglobin level, and urinary albumin to creatinine ratio.

Patients and Methods*:* 70 patients were enrolled in this study. Patients were divided into 35 diabetic patients without CKD and 35 diabetic patients with CKD at the Kidney clinic/Nephrology Unit and Centre of diabetes and diabetic foot, Department of Internal Medicine, Assiut University Hospitals, in the period from October 2019 to July 2022. Patients who had other causes of peripheral vascular disease were excluded.

Results*:* There was a statistically significant increase in the percentage of gangrene and amputation in the diabetic CKD group (31.4%) and (51.4%) when compared with the diabetic non-CKD group (11.4%) (14.3%). Foot ulcers were mainly ischemic and neuroischemic ulcers in diabetic CKD patients (57% of ulcers). In diabetic CKD, there was a significant Positive correlation between ABI and eGFR and a significant Negative correlation between ABI and (Ca, pH, and PTH).

Conclusion: In diabetic CKD patients, ischemic types of diabetic foot (gangrene, amputation, ischemic and neuroischemic ulcer) and PAD were significantly increased when compared with diabetic non-CKD patients. Estimated GFR and serum phosphorus level were the most significant predictors of peripheral arterial disease in diabetic CKD patients.

Keywords: CKD; Diabetic foot, Ischemic.

Introduction:

Chronic kidney disease is an important contributor to morbidity and mortality. The global prevalence of CKD was 9.1% (697.5 million cases) in 2017 [1].

Diabetes is a leading cause of end-stage renal disease worldwide [2]. Foot abnormalities and amputation are major health concerns as they diminish health-related quality of life and cause financial burden [3].

KDIGO 2020 defines chronic kidney disease (CKD) as persistently elevated urine albumin excretion (≥ 30 mg/g [3mg/mmol]

creatinine), reduced estimated glomerular filtration rate (eGFR < 60 ml/min per 1.73 m2), or both, for greater than 3 months [4].

Diabetic foot is defined as either diabetic peripheral neuropathy, peripheral arterial disease, infection, ulceration, or Charcot osteoarthropathy, or a combination of these abnormalities, in a person diagnosed with diabetes mellitus, according to the guidelines of the International Working Group of Diabetic Foot 2020 (IWGDF) [5].

There is a much higher incidence of diabetic foot disorder in those with renal disease, and outcomes are generally poorer [2] as CKD patients share three main risk factors of foot ulceration and amputation: neuropathy, peripheral arterial disease, and increased susceptibility to infection with impaired wound healing [6].

This research is conducted as little is known about the potential relationship between chronic kidney disease and diabetic foot. This research evaluates diabetic foot lesions (especially ischemic type) in CKD patients and the factors that may aggravate them in CKD, to inform future needs to modify our clinical policies in managing ischemic diabetic foot in CKD patients to provide a better prognosis and prevent long-term disabilities.

Patients and Methods

Seventy patients were enrolled in this study. Patients were divided into 35 diabetic patients without CKD and 35 diabetic patients with CKD at the Kidney clinic/Nephrology Unit and Centre of diabetes and diabetic foot, Department of Internal Medicine, Assiut University Hospitals, in the period from October 2019 to July 2022. Patients who had other causes of peripheral vascular disease were excluded.

Methodology:

Full history taking includes: demographic data (name, age, residence), type and duration of diabetes (type 1 and type 2), stage and duration of CKD, history of previous cardiovascular or cerebrovascular disease, foot ulceration, amputation, Charcot's joint and vascular surgery, neuropathic symptoms (sensory loss, numbness, paraesthesia, spontaneous pain, increased sensation of pain, pins-and-needles pain and vascular symptoms Intermittent claudication, rest pain, non-healing ulcer and venous insufficiency.

Full Clinical examination*:* Anthropometric measurements, blood pressure, and foot examination. Foot examination according to the International Working Group on the Diabetic Foot (IWGDF 2019) includes:

1. **Inspection** of skin status, nail pathology, infection, ulceration, calluses/ blistering, deformity, muscle wasting, joint stiffness, amputation, and fissures.
2. **Palpation** of temperature, capillary refill time (should be less than 2 seconds)
3. **Neurological assessment by:**
   - Monofilament test.
4. **Vascular assessment**
   - Foot pulse
   - Ankle-brachial index (ABI) is a non-invasive method to evaluate peripheral artery disease (PAD), which is obtained by dividing the systolic blood pressure measured at the ankle by the brachial systolic blood pressure. Results from 0.9 to 1.3 are normal. Values less than 0.8 indicate PAD, and those greater than 1.3 indicate a major form of arteriosclerosis with complete calcification of the tunica media.
   - Type of ulcer: ischemic, neuropathic, or mixed.
5. **Motor assessment**

   Assess all active and passive movements of the foot.

Investigations:

X-ray of the foot**,** Hemoglobin A1C, Complete blood picture, Kidney function tests, Urine analysis, Estimated Glomerular filtration rate by The CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation, Urinary Albumin/creatinine ratio, Total protein, Serum albumin, Alkaline phosphatase, Serum calcium, phosphorus and potassium, Parathyroid hormone, Serum uric acid and C-reactive protein.

Statistical Analysis:

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 24. Qualitative data were expressed as frequency and percentage. Quantitative data were expressed as mean (±SD). The following tests were done: Mann-Whitney U test (MW) when comparing between two groups (for non-normally distributed data), Chi-square test was used when comparing between non-parametric data, Univariate analysis, linear regression, and Probability (P-value), which was considered significant if it was < 0.05.

Ethical Considerations:

Assiut Faculty of Medicine approved the methodology and the study design (IRB number is 17101368). The research volunteers gave their signed informed consent before beginning the study. The entire study was conducted confidentially. The study's subjects were not exposed to any risks, and whether or not they participated in the study had no bearing on the quality of the healthcare they received.

RESULTS

Table (1): Maximum score of 10 points. People with an NDS of six points or more are considered to show abnormality.

Neuropathy Disability Score (NDS) [7]		**Right**	**Left**
Vibration Perception Threshold 128-HZ tuning fork; apex of big toe: normal = can distinguish vibrating / not vibrating	Normal = 0 abnormal = 1		
Temperature Perception on the Dorsum of the Foot Use a tuning fork with a beaker of ice / warm water.			
Pin-Prick Apply the pin proximal to the big toenail just enough to deform the skin. Trial pair = sharp, blunt; Normal = can distinguish sharp \ not sharp			
Achilles Reflex	Present = 0 Present with reinforcement = 1 Absent = 2		
	NDS Total out of 10		

Table (2): Basic characteristic data of studied groups

		Diabetic CKD (N = 35)		Diabetic non-CKD (N = 35)		Stat. test	P-value
Age (years)	Mean	51.9		53.9		T = 0.62	0.534
	±SD	12.8		13.6			
Sex	Male	20	57.1%	21	60%	X^2 = 0.059	0.808
	Female	15	42.9%	14	40%		
Residence	Rural	22	62.9%	26	74.3%	X^2 = 1.06	0.303
	Urban	13	37.1%	9	25.7%		
BMI (kg/m²)	Mean	22.6		26.7		T = 3.7	< 0.001
	±SD	4.2		4.8			
Type of DM	Type I	10	28.6%	5	14.3%	X^2 = 2.12	0.145
	Type II	25	71.4%	30	85.7%		
Duration of DM (years)	Mean	16.3		13.9		T = 1.33	0.185
	±SD	7.0		7.7			
Treatment of DM	Oral hypoglycemic drugs	17	48.6%	23	65.7%	X^2 = 2.1	0.147
	Insulin	18	51.4%	12	34.3%		
Systolic Blood Pressure (mmHg)	Mean	123.1		125.1		0.56	0.575
	±SD	16.4		13.1			
Diastolic Blood Pressure (mmHg)	Mean	79.1		80.9		0.62	0.534
	±SD	12.5		10.4			
Mean pressure (mmHg)	Mean	120.1		120.2		0.02	0.984
Duration of CKD (years)	Mean ±SD	5.8 ± 1.76		-		-	-
	Min - Max	2 – 10		-			
CKD stage	Stage III	8	22.9%	-		-	-
	Stage IV	11	31.4%				
	Stage V	16	45.7%				

T: Independent sample T test.
X2: Chi-square test.
DM: diabetes mellitus.
BMI: body mass index.
S: p-value < 0.05 is considered significant.
NS: p-value > 0.05 is considered non-significant.
CKD: chronic kidney disease.

Table (2) showed no statistically significant difference between the studied groups regarding all basic characteristic data. However, there was a statistically significant decrease in BMI in the diabetic CKD group compared to the diabetic non-CKD group (p-value < 0.001 S). Diabetic CKD patients were divided into stages III, IV, and V with percentages of 22.9%, 31.4%, and 45.7%, respectively.

Table (3): Comparison of studied laboratory data between the studied groups.

		Diabetic CKD		Diabetic non-CKD		T	P-value
Complete blood count							
Hemoglobin (g/dl)	Mean ±SD	9.3	± 1.4	12.2	± 1.3	8.7	< 0.001
MCV (fl/cell)	Mean ±SD	76.4	± 6.2	79.4	± 5.5	2.15	0.035
MCH (pg/cell)	Mean ±SD	25.3	± 2.6	26.9	± 2.3	2.65	0.01
WBCs (x10³/l)	Mean ±SD	11.5	± 4.6	9.05	± 4.1	2.3	0.024
platelet (x10³/ul)	Mean ±SD	245.3	±92.3	290.9	±104.6	1.93	0.057
Chemistry & Electrolytes							
Potassium (mmol/L)	Mean ±SD	5.3	± 0.7	4.2	± 0.6	6.7	< 0.001
Calcium (mg/dl)	Mean ±SD	8.1	± 1.3	8.9	± 0.5	3.38	0.001
Phosphorus (mg/dl)	Mean ±SD	6.0	± 1.6	4.0	± 0.7	6.88	< 0.001
Uric acid (mg/dl)	Mean ±SD	7.2	± 1.6	6.7	± 1.6	1.22	0.224
Total protein (mg)	Mean ±SD	60.4	± 3.9	68.7	± 4.9	7.818	< 0.001
Albumin (mg)	Mean ±SD	33.9	± 3.5	37.4	± 3.4	4.2	< 0.001
Alkaline phosphatase (IU/L)	Mean ±SD	161.4	± 61.7	85.3	± 25.6	6.7	< 0.001
Lipid profile (mg/dl)							
Triglyceride	Mean ±SD	201.5	± 93.8	185.4	± 66.9	0.82	0.411
Cholesterol	Mean ±SD	182.7	± 64.2	198.8	± 57.9	1.1	0.275
Low-density lipoprotein	Mean ±SD	112.7	± 37.5	117.3	± 56.5	0.4	0.689
High-density lipoprotein	Mean ±SD	27.1	± 5.1	31.9	± 8.0	2.98	0.004
Very low-density lipoprotein	Mean ±SD	51.8	± 27.8	55.7	± 15.2	0.74	0.461
Urine analysis							
Urine analysis	Normal	0	0%	35	100%	X^2= 70	< 0.001
	Proteinuria	35	100%	0	0%		
ALB/ CR ratio(mg/g)	Mean ±SD	534.2	±313.9	15.1	± 3.7	9.78	< 0.001
Category of albuminuria	No albuminuria	0	0.0%	35	100%	X^2= 70.0	<0.001
	Microalbuminuria	6	17.1%	0	0.0%		
	Macroalbuminuria	29	82.9%	0	0.0%		
Hormone							
Parathyroid hormone (pg/ml)	Mean ±SD	699.3	±471.9	51.7	±12.2	8.1	< 0.001
Others							
HbA1C (%)	Mean ±SD	7.1	± 0.6	8.5	± 1.4	5.1	< 0.001
C-reactive protein (mg/L)	Mean ±SD	16.5	± 19.9	11.7	± 11.4	1.25	0.215

T: Independent sample T test. **S:** p-value < 0.05 is considered significant.
X2: Chi-square test. **NS:** p-value > 0.05 is considered non-significant.

Table (3) showed:

- Statistically significant decreased Hb, MCV, MCH, HbA1C, ALB, HDL, and Ca in the diabetic CKD group when compared with the diabetic non-CKD group.
- Statistically significant increased WBCs, ALP, Ph, PTH, and ALB/CR ratio in the diabetic CKD group when compared with the diabetic non-CKD group.

- There was no statistically significant difference between the studied groups with regard to other laboratory data.
- Regarding the category of albuminuria in diabetic CKD patients, all had a degree of albuminuria; 17 % had microalbuminuria, and 83 % had macroalbuminuria.

Table (4): Comparison of diabetic foot abnormalities between the studied groups.

Foot abnormality		Diabetic CKD (N = 35)		Diabetic non-CKD (N = 35)		X^2	P-value
Foot deformity		12	34.3%	10	28.6%	0.26	0.607
Foot deformity type	Flat foot	5	41.7%	3	30%	0.56	0.452
	Pes Cavus	1	8.3%	4	40%	1.93	0.163
	Charcot foot	3	25%	1	10%	1.06	0.303
	Toes deformities	3	25%	2	20%	0.21	0.642
Amputation		18	51.4%	5	14.3%	10.9	0.001
Ulcer		21	60%	26	74.3%	1.6	0.203
Ulcer type	Neuropathic	9	42.9%	20	76.9%	7.1	0.008
	Ischemic	5	23.8%	0	0.0%	7.3	0.007
	Neuroischemic	7	33.3%	6	23.1%	0.5	0.495
Gangrene		11	31.4%	4	11.4%	4.1	0.041
Interdigital fungal infection		3	8.6%	4	11.4%	0.15	0.690
Diabetic foot infection		32	91.4%	25	71.4%	3.08	0.065

X2: Chi-square test. **S:** *P*-value < 0.05 is considered significant.
NS: *P*-value > 0.05 is considered non-significant.

Table (4) showed:

- There was no statistically significant difference between the studied groups with regard to foot deformities, interdigital fungal infection, or diabetic foot infection. Still, Charcot foot was 25% in the diabetic CKD patients vs 10% in non-CKD patients.
- The percentage of foot infections was higher in the diabetic CKD group (91.4%) than in the diabetic non-CKD group (71.4%).
- There was a statistically significant increase in the percentage of gangrene and amputation in the diabetic CKD group (31.4%) and (51.4%) when compared with the diabetic non-CKD group (11.4%) (14.3%).
- There was no statistically significant difference between the studied groups with regard to foot ulcers. However, the percentage of ulcers was higher in diabetic non-CKD patients than in diabetic CKD patients. Foot ulcers were mainly neuropathic ulcers in diabetic non-CKD patients (77% of ulcers) and ischaemic/neuroischaemic ulcers in diabetic CKD patients (57%)

Table (5): Comparison of assessment of peripheral arterial disease between the studied groups.

		Diabetic CKD (N = 35)		Diabetic non-CKD (N = 35)		Stat. test	P-value
Foot pulsations	Absent	14	40%	8	22.9%	$X^2 = 2.38$	0.122
	Preserved	21	60%	27	77.1%		
Ankle Brachial Index (ABI)	Mean	0.66		0.83		T = 3.6	< 0.001
	±SD	0.21		0.17			
Vascular calcification by X-ray	No	25	71.4%	35	100%	$X^2 = 11.6$	0.001
	Yes	10	28.6%	0	0%		
Peripheral arterial disease (PAD)	No	14	40.0%	24	68.6%	$X^2 = 5.8$	0.016
	Yes	21	60.0%	11	31.4%		

X2: Chi-square test. **S:** *P*-value < 0.05 is considered significant.
NS: *P*-value > 0.05 is considered non-significant.

Table (5) showed:

- There was no statistically significant difference between the studied groups with regard to peripheral pulsations.
- ABI was statistically significantly decreased in the diabetic CKD group (0.66 ± 0.21) compared to the diabetic non-CKD group (0.83 ± 0.17).
- There was a statistically significant increase in the percentage of vascular calcification by x-ray in the diabetic CKD group (10 patients, 28.6%) compared to the diabetic non-CKD group (0 patients, 0%).
- Statistically significant increased percentage of PAD (ABI less than 0.8 according to WIFI classification) in the CKD group (21 patients, 60%) when compared with the non-CKD group (11 patients, 31.4%).

Table (6): Correlation study between ABI and other studied data in the Diabetic CKD group

	ABI	
	R	***P*-value**
Age	-0.27	0.108
Mean Blood Pressure	-0.09	0.591
CKD duration	-0.04	0.790
DM duration	0.1	0.561
eGFR	0.71	<0.001
Potassium	0.11	0.517
Uric acid	0.13	0.47
Calcium	-0.45	0.006
Phosphorous	-0.58	<0.001
Parathyroid hormone	-0.50	0.002
Albumin	-0.08	0.617
Albumin\creatinine ratio	-0.29	0.085
Hemoglobin level	0.28	0.098

(r): Pearson correlation coefficient. **S:** p-value < 0.05 is considered significant.
NS: p-value > 0.05 is considered non-significant. **eGFR:** estimated glomerular filtration rate.

Table (6) showed:

- Statistically significant Positive correlation between ABI and eGFR.
- Statistically significant Negative correlation between ABI and (Ca, pH, and PTH).
- No statistically significant correlation between ABI and other studied data.

Table (7): Correlation study between ABI and other studied data in the diabetic non-CKD group.

	ABI	
	R	***P*-value**
Age	- 0.48	0.003
Mean BP	- 0.53	0.001
DM duration	- 0.1	0.564
K	0.17	0.333
UA	0.18	0.301
Ca	0.14	0.434
Phosphorous	0.23	0.18
PTH	0.20	0.248
ALB	0.17	0.324
Hb	0.03	0.868

Table (7) showed:

- As regards ABI correlations in the diabetic non-CKD group, there were:
- Statistically significant negative correlation between ABI and age and mean arterial blood pressure.
- No statistically significant correlation between ABI and other studied data.

Table (8): Univariate linear regression of ABI in diabetic CKD group.

	Ankle Brachial Index (ABI) (diabetic CKD group)			
	EXB	**95.0% Confidence Interval for B**		**P. value**
		Lower	**Upper**	
eGFR	5.905	0.006	0.013	0.000
Calcium	-2.954	-0.130	-0.024	0.006
Phosphorous	-4.140	-0.113	-0.039	0.000
Parathyroid hormone	-3.376	0.000	0.000	0.002

(R): Pearson correlation coefficient. S: p-value < 0.05 is considered significant.
NS: p-value > 0.05 is considered non-significant.
-eGFR: estimated glomerular filtration rate.

Table (8) showed:

- eGFR was significantly associated with the ABI score after adjustment for other factors. ABI decreases by 5.90 with the decrease of eGFR (beta = 5.9, 95% * CI = (0.006/0.013) in diabetic CKD patients.
- Serum phosphorus was significantly associated with the ABI score after adjustment for other factors. ABI decreases by 4.1 with increased serum phosphorus level (beta= 4.1,95%* CI= (0.113\0.03) in diabetic CKD patients.
- PTH was associated significantly with the ABI score after adjustment for other factors. ABI decreases by 3.37 with the increase of PTH (beta=3.37,95% * CI= (0.000\0.000) in diabetic CKD patients.
- Serum Ca was associated significantly with the ABI score after adjustment for other factors. ABI decreases by 2.95 with increased serum Ca level (beta=2.95,95%* CI=0.130\0.024) in diabetic CKD patients.

Table (9): Univariate linear regression of ABI in the diabetic non-CKD group.

	Ankle Brachial index (ABI) (diabetic non-CKD)			
	EXB	95.0% Confidence Interval for B		P. value
		Lower	Upper	
Age	-0.485	-0.01	-0.002	0.003
Mean Blood Pressure	-3.660	-0.009	-0.002	0.001

Univariate linear regression. **S:** p-value < 0.05 is considered significant.
NS: *P*-value > 0.05 is considered non-significant.

Table (9) showed:

- Mean arterial blood pressure was significantly associated with the ABI score after adjustment for other factors. ABI decreases by 3.66 with the increase of mean arterial blood pressure (beta = 3.66, 95% * CI = (- 0.009/- 0.002).
- Age was significantly associated with the ABI score after adjustment for other factors. ABI decreases by 0.485 with the increase of age (beta = 0.485, 95% * CI = (-0.01/- 0.002).

Discussion

Diabetic foot disease is the most serious complication of diabetes mellitus [8]. CKD patients are sharing three main risk factors of foot ulceration and amputation: neuropathy, peripheral arterial disease, and increased susceptibility to infection with impaired wound healing [9].

This study focused on ischemic type diabetic foot abnormalities in CKD patients and those without CKD. In addition, it studied the factors that may aggravate foot ischemia in both groups.

The studied groups, diabetic CKD and diabetic non-CKD, showed no significant difference regarding baseline characteristics (age, sex, residence, blood pressure, type of diabetes, duration of diabetes, and treatment of diabetes); however, CKD patients had a lower BMI than the non-CKD group. This is because CKD is a debilitating disease associated with malnutrition and malabsorption [10] and a high catabolic rate [11].

Studied cases had nephropathy (elevated serum creatinine and/or albuminuria), and all controls had no nephropathy, which was compatible with the selection criteria of the current study.

Diabetic foot ulcers were more common in diabetic non-CKD patients than in diabetic CKD patients. It was hypothesized that ESRD patients had some degree of disability, and dialysis is often associated with loss of work [9], so ESRD patients were less susceptible to foot trauma and ulcers.

Ulcers were mainly neuropathic (77% of ulcers) in diabetic non-CKD patients, while in diabetic CKD patients, ulcers were mainly ischemic and neuro-ischemic (57% of ulcers). Since most diabetic patients had neuropathy, the presence of a pure ischemic ulcer was uncommon in the studied groups.

The most accurate method to evaluate PAD or foot ischemia is ABI, as not all patients with PAD have absent foot pulsations. However, all patients with PAD had abnormal ABI.

The results showed a significant increase in PAD and vascular calcifications on X-ray in diabetic CKD patients compared to diabetic non-CKD patients.

In addition, there was a significant positive correlation between ABI and eGFR in the diabetic CKD group, which means decreased eGFR is associated with decreased ABI and more PAD. This might be explained by uremic toxins[12], hyperparathyroidism[13], hyperphosphatemia[14], and vascular calcifications[14], that is in agreement with the results of the current study which showed that there was a significant increase in Ph, ALP, and PTH in the diabetic CKD group compared to diabetic non-CKD group. The CKD group had a significant negative correlation between calcium, phosphorus, and parathyroid hormone and ABI. Univariate analysis showed that the most significant predictors of PAD in diabetic CKD patients were eGFR and serum phosphorus level.

The pathogenesis of PAD in CKD patients differs from that of PAD in patients without CKD. This may be explained by three mechanisms: the first mechanism is that high PTH increases bone resorption that results in increased blood phosphorus and calcium[15], The second mechanism is that the increased Ph leads to increased expression of Runx-2 (which is a gene that regulates proliferation and differentiation of osteoblasts) and changes the smooth muscle cells in the walls of blood vessels into osteoblast-like cells[16], The third mechanism is increased ALP, which will increase the degradation of pyrophosphate, an inhibitor of vascular calcification, which leads to hydroxyapatite deposition and arterial calcification[16].

In CKD patients, PAD is not associated with typical dyslipidemia as most of CKD patients had normal lipid profile and the only lipid change that appears to be related to CKD patients is a decrease in plasma HDL levels and HDL dysfunction, which is anti-inflammatory, antioxidant, and has a protective function against atherosclerosis[17], this matched with the current study results which showed that there was no significant difference between the studied groups regarding all components of the lipid profile except HDL, which showed a significant decrease in the CKD group compared to the non-CKD group.

In the diabetic non-CKD group, there was a significant negative correlation between ABI and age and mean arterial blood pressure, which is matched with other studies that found that old age and hypertension are risk factors for PAD [18].

Our study acknowledges limitations, such as a relatively small sample size and being conducted in a single center. Still, our study discussed diabetic foot in CKD patients, excluding other causes of peripheral arterial disease, which was a weak point in other studies.

Conclusion

In diabetic patients with CKD, the ischemic type of diabetic foot and peripheral arterial disease was significantly increased when compared with diabetic patients without CKD. Estimated GFR and serum phosphorus level were the most significant predictors of peripheral arterial disease in diabetic CKD patients.

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