ORIGINAL ARTICLE

Renal function is highly associated with podiatric risk in diabetic patients

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ABSTRACT

Background. Chronic kidney disease (CKD) is correlated with the incidence of diabetic foot ulcer (DFU). Furthermore, the International Working Group on the Diabetic Foot (IWGDF) has proposed a classification of the risk factors for DFU. The purpose of this study was to investigate the relationship between the IWGDF risk classification and the glomerular filtration rate level estimated by the CKD Epidemiology Collaboration formula (eGFR).

Methods. We conducted a prospective multicentric study. Patients were recruited from either diabetology or nephrology departments. The secondary objectives were to determine this relationship after excluding people on dialysis and to identify the factors associated with podiatric risk.

Results. Four hundred and eighty-six patients were included, with a mean age of 64.2 years ($\pm$15.7) and a mean diabetes duration of 15.7 years ($\pm$12.1). Based on the IWGDF classification, 53.5% of the population were in podiatric stage 0, 11.7% in stage 1 and 34.8% in stage 2 or 3. The mean eGFR level was significantly lower in patients with podiatric risk $\geq$2 (36.8 $\pm$ 33.9 mL/min/1.73 m^2 vs 71.9 $\pm$ 35.3 mL/min/1.73 m^2, $P < .0001$) and a significant association was found between the eGFR and the podiatric risk. This association remained significant after the exclusion of the hemodialysis patients. After receiver operating characteristic analysis, a cutoff of 45 $\pm$ 11 mL/min/1.73 m^2 (area under the curve 0.76) was found discriminant to define a group of CKD patients at higher risk for podiatric stage $\geq$2.

Conclusion. eGFR levels are linked to podiatric stages in diabetes mellitus. Patients with eGFR <45 mL/min/1.73 m^2 and dialysis patients should be carefully managed in collaboration with diabetic foot specialized centers.

LAY SUMMARY

Chronic kidney disease has been correlated with an increased incidence of diabetic foot ulcer (DFU). However, there are no data describing the relationship between the risk score for DFU, which has been built in a logic of prevention, and the level of renal function. Therefore, the purpose of this prospective multicentric study was to describe the association between renal function and the risk of DFU using the International Working Group on the Diabetic Foot classification. Four hundred and eighty-six patients were included. In multivariate analysis, the podiatric risk stage was associated with eGFR and albuminemia. After receiver operating characteristic analysis, the Youden index best

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estimating the risk of reaching a high podiatric stage ≥ 2 was 45 ± 11 mL/min/1.73 m^2 [area under the curve (AUC) 0.76] for the entire population and 68 ± 6 mL/min/1.73 m^2 (AUC 0.70) after excluding hemodialysis patients. This study reinforces the arguments for joint work between nephrologists and diabetologists, and setting up alert thresholds that can be used in routine clinical practice.

INTRODUCTION

Diabetes mellitus (DM) is the main cause of chronic kidney disease (CKD) and non-traumatic lower limb amputation [1]. Moreover, 19%–34% of diabetic patients will develop a diabetic foot ulcer (DFU) in their lifetimes [2]. In 2017, people living with diabetes made up 49.6% of the dialysis population in the USA [3]. Diabetic patients with CKD and/or DFU are therefore a major public health concern. Furthermore, in 2017, amputation and end-stage renal disease accounted for a Medicare expenditure of 36 billion US dollars [4].

CKD has been correlated with an increased incidence of DFU [5], and the initiation of dialysis seems to be a consequential step [6]. Furthermore, the prognosis for DFU in the context of CKD is quite poor [7–9]. Healing, amputation and mortality are all affected by CKD with an estimated glomerular filtration rate (eGFR) <90 mL/min/1.73 m^2 [10]. Further, the mortality relative risk for patients with DFU and CKD is dramatically higher than that for people without CKD, with an increased risk between 1.22 [11] and 3.54 [10]. Last, CKD G5D (dialysis patients) is associated with DFU incidence and prognosis [12], notably in terms of amputation risk and mortality after amputation, with a mortality rate of 50%–70% 1 year after amputation [13].

In 1999, the International Working Group on the Diabetic Foot (IWGDF) suggested a way to assess the risk of DFU in diabetic patients, which is today in routine use. Since 2019, the IWGDF has included CKD G5D in its classification [14]. This update paralleled a similar decision of the National Institute for Health and Care Excellence (NICE) [15], which added CKD G5D to its own podiatric risk classification in 2015. To our knowledge, however, there are no data describing the relationship between the risk score for DFU and the level of renal function, yet this information is essential for implementing adapted DFU prevention measures.

Therefore, the twofold purpose of this study was to describe the association between renal function and the risk of DFU using the IWGDF classification, and to determine whether there is a threshold effect in this relationship. Predictive factors associated with the podiatric risk were also analyzed.

MATERIALS AND METHODS

We conducted a prospective observational multicenter study. All patients received written information about the study and none presented opposition. The study was reviewed and approved by the Institutional Review Board of the University Hospital of Montpellier, France (identification number: 2019_IRB-MTP_09–12; clinical trial: NCT04100551).

Patients

The study was proposed to all outpatients with DM followed by the diabetology department of Montpellier University Hos-pital. Only consulting patients were recruited in order to maintain our focus on stable CKD. Patients on dialysis were recruited in the dialysis centers of the University Hospital of Montpellier and in Nephrocare, a private hospital in Montpellier. All patients were over 18 years old and none was under conservatorship. Patients with a previous solid organ transplant of any kind were excluded.

Data collection

Basic characteristics such as gender, age, height, weight, body mass index (BMI), type and length of diabetes, diabetic complications and current treatments were collected. Diabetes balance was evaluated according to HbA1c. Blood pressure was classified as: high blood pressure but at or under the objective while under treatment according to the European Society of Hypertension, high blood pressure exceeding the objective, and no high blood pressure [16]. Albuminuria was expressed by the albuminuria/creatinuria ratio.

Routine biological explorations were made concomitant to creatinine measurement: hemoglobin (Hb), C-reactive protein (CRP), urea, magnesium, uric acid, sodium, potassium, bicarbonate (HCO3$^-$), albumin, calcium, phosphorus, 25-OH-vitamin D, parathyroid hormone and blood lipid parameters [triglycerides, total cholesterol, calculated or measured low-density lipoprotein (LDL) and high-density lipoprotein (HDL)].

Podiatric risk classification

Podiatric risk classification followed the 2019 IWGDF guidelines as follows: stage 0, no neuropathy; stage 1, peripheral neuropathy or peripheral artery disease (PAD); stage 2, peripheral neuropathy (PND) with PAD and/or foot deformity; and stage 3, peripheral neuropathy or PAD with previous foot ulcer, lower-extremity amputation or CKD G5D (Supplementary data, Table S1) [14]. Given the study objective, we did not automatically categorize the patients with CKD G5D as having podiatric stage 3 in order to study the diversity and distribution of the stages within this population. This decision allowed us to exhaustively examine the whole population with CKD.

Renal function evaluation

Blood creatinine was measured by enzymatic techniques in all patients at least 3 months before and not more than 3 months after the podiatric classification. The GFR was estimated (eGFR) by the CKD Epidemiology Collaboration (CKD-EPI) equation. The association between the eGFR and the IWGDF score was the main endpoint of this study and the patients were divided into groups according to the eGFR level used in the CKD classification (eGFR ≥ 90 mL/min/1.73 m^2, between ≥ 60 and <90 mL/min/1.73 m^2, between ≥ 45 and <60 mL/min/1.73 m^2, between ≥ 30 and <45 mL/min/1.73

m^2, between ≥15 and <30 mL/min/1.73 m^2, <15 mL/min/1.73 m^2 with or without dialysis, and CKD G5D for those patients on dialysis). If a patient was on dialysis, we asked for the length of time on renal replacement therapy and the value given to the eGFR was "0 mL/min/1.73 m^2."

Statistical analysis

Non-normality of the distributions of the numerical variables was detected by the Q-Q plot and the Shapiro–Wilk test. The variables were described using mean ± standard deviation (SD), the median and interquartile range, or percentage, depending on their distribution.

Prior to analysis, the association between missingness and baseline variables was tested in a logistic regression (data not shown). A significant association with eGFR indicated that our data were not missing completely at random, and missing at random (MAR) may be a more plausible assumption under which to conduct further analysis.

Patients were divided into groups according to their podiatric stage. The podiatric risk classification was highly skewed and, to limit the efficiency loss and bias on estimates of the regression coefficients, the main outcome was analyzed as an ordered categorical response. We assigned the numerical value of the classification scale for the ordered categories (c = 0, 1, 2, 3). Generalized linear mixed models (GLMM) for analyzing multilevel ordinal categorical responses were used. Under MAR condition, mixed models offer an alternative to handle missing data without requiring imputations. GLMM were constructed for each explanatory variable with a random intercept and an unstructured-covariance matrix. Multivariate modeling was performed using the significant variables found at the univariate level. The models were compared by the likelihood ratio test in order to obtain the most simplified final model. Two final models were described, depending on whether patients on dialysis were kept or not. Pairwise comparisons were performed if necessary with the Tukey SHD.

We conducted a second analysis to compare the characteristics of the patients with high podiatric risk (stage ≥2) vs low podiatric risk (stage <2) [17]. The comparisons between groups were performed by the T-test, the Wilcoxon rank sum test or the χ^2 test as appropriate and GLMMs for analyzing binomial responses were used the most simplified model was obtained using the same methodology as previously described. Two final models were also constructed, depending on whether patients on dialysis were kept or not.

To assess the robustness of our findings, we finally conducted a sensitivity analysis in which the association between eGFR and the podiatric stage was tested in a complete case analysis (106 non-dialysis patients) using the same statistical procedure.

We finally used a receiver operating characteristic (ROC) analysis to evaluate the Youden index to account for the potential discriminating ability of eGFR to define a group of CKD patients at higher risk for podiatric stage ≥2.

All statistics were performed using Stata14 (Statacorp, College Station, TX, USA) and Prism 8 (Graphpad Software). A P < .05 was considered as significant.

RESULTS

Description of the population

Four hundred and eighty-six patients were included between 1 November 2019 and 31 May 2021. The clinical characteristics of

Table 1: Clinical characteristics of patients.

Variable	Number of available data	
Age (years)	486	64.2 (±15.6)
Female [*n* (%)]	486	168 (34.6)
Diabetes duration (years)	471	15.7 (±12.1)
Diabetes type	486	
Type 2 [*n* (%)]		408 (84.0)
BMI (kg/m^2)	477	29.1 (±5.7)
Diabetes complications [*n* (%)]		
Diabetic retinopathy	486	100 (20.6)
Ischemic heart disease	486	118 (24.3)
Stroke history	486	38 (7.8)
Patient under diabetic treatment		453 (93.2)
Biguanide users		204 (41.2)
Sulfonylurea and glinides		106 (21.8)
GLP-1 analogs users		105 (21.6)
Insulin users		289 (59.5)
Lipid-lowering treatments users		290 (59.7)
Antihypertensive drugs		360 (74.1)
IWGDF 2019 grade [*n* (%)]	486	
0		260 (53.5)
1		57 (11.73)
2		72 (14.81)
3		97 (19.96)
Kidney parameters	486	
eGFR (mL/min/1.73 m^2)		59.7 (±38.6)
CKD stage (%)	486	
>90 mL/min/1.73 m^2		143 (29.4)
60–90 mL/min/1.73 m^2		100 (20.6)
45–60 mL/min/1.73 m^2		51 (10.5)
30–45 mL/min/1.73 m^2		70 (14.4)
15–30 mL/min/1.73 m^2		53 (10.9)
<15 mL/min/1.73 m^2 or dialysis		69 (14.2)
Dialysis		56 (11.5)
Dialysis duration (days)	56	1320 (±1060)
Biology		
Mean HbA1c (%)	485	7.6 (±1.5)
Albuminuria/creatinuria (mg/g)	195	292 (±910)
Calcemia (mmol/L)	327	2.44 (±0.16)
Phosphoremia (mmol/L)	305	1.18 (±0.39)
Parathyroid hormone (pg/mL)	191	187 (±269)
Albuminemia (g/L)	330	41.4 (±4.7)
Hemoglobin (g/dL)	430	13.4 (±5.9)
LDL-cholesterol (mmol/L)	359	2.28 (±0.93)
HDL-cholesterol (mmol/L)	342	1.22 (±0.41)

Data are presented as number (%) or mean (±SD).

the whole population are shown in Table 1. Mean age was 64.2 years (±15.7) and mean diabetes duration was 15.7 years (±12.1). Eighty-four percent of the population had type 2 diabetes, with 77.6% having BMI >25 kg/m^2 and 42.8% BMI >30 kg/m^2. More than half the population (59.5%) was treated with insulin.

According to the podiatric classification, 53.5% of the patients were stage 0, 11.7% stage 1, 14.8% stage 2 and 20% stage 3.

According to eGFR levels, 143 (29.4%) presented an eGFR >90 mL/min/1.73 m^2, 100 (20.6%) were between ≥60 and <90 mL/min/1.73 m^2, 51 (10.5%) were ≥45 and <60 mL/min/1.73 m^2, 70 (14.4%) were ≥30 and <45 mL/min/1.73 m^2, 53 (10.9%) were ≥15 and <30 mL/min/1.73 m^2, and 70 (14.4%) were <15 mL/min/1.73 m^2. Fifty-six (11.5%) were on dialysis. All the clinical and biological characteristics of the whole group are presented in Table 1.
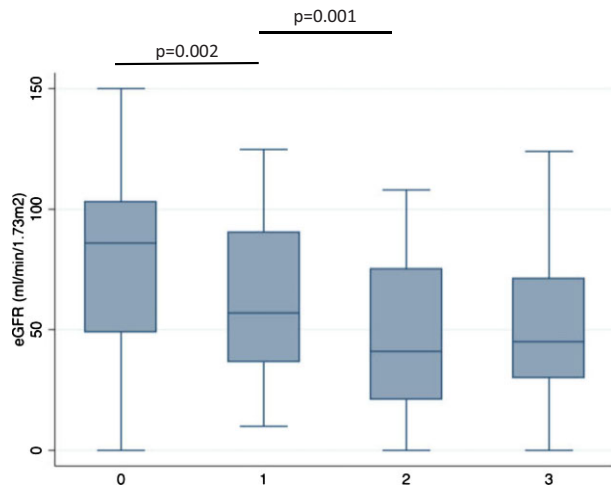
Figure 1: Mean eGFR according to the 2019 IWGDF podiatric risk of the non-dialysis patient.
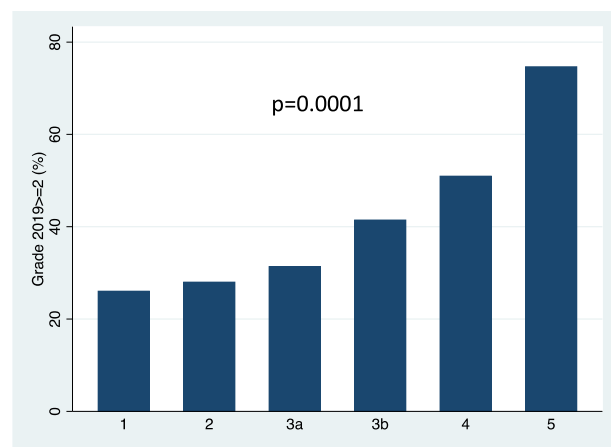

Figure 2: Proportion of patient with a 2019 IWGDF podiatric grade ≥2 according to the eGFR level without dialysis patients.

Association between eGFR level and podiatric risk

In non-dialysis patients, the mean eGFR was 76.4 ± 33.7, 62.3 ± 30.3, 48.2 ± 30.1 and 51.7 ± 29.7 mL/min/1.73 m^2, respectively, in podiatric risk stage 0, 1, 2 and 3. There was a significant difference between podiatric risk stage 0 and 1 (P = .02), 1 and 2 (P < .001), and 1 and 3 (P < .001), but not between 2 and 3 (Fig. 1). Furthermore, the prevalence of podiatric risk stage ≥2 increased with the worsening of the renal function (P = .0001) (Fig. 2).

Factors associated with the podiatric risk classification

In the univariate analysis, the risk stage was associated with creatininemia, eGFR, dialysis, dialysis duration, albuminuria/creatinuria ratio, BMI, biguanide use, DPP4-inhibitor or insulin treatment, the completion of a retinographic check-up within the year, the balance of high blood pressure, magnesemia, HCO3$^-$, CRP and LDL-cholesterol (Table 2 and Supplementary data, Table S2).

In the multivariate analysis, when dialysis patients were included, eGFR (β = –0.013 ± 0.0017, P < .0001) and albuminemia ((β = –0.039 ± 0.014, P = .007) were associated to podiatric risk. After exclusion of the dialysis patients, only eGFR (β = –

0.012 ± 0.003, P < .0001) remained associated with podiatric risk (Table 3).

Factors associated with high podiatric risk

High podiatric risk (stage ≥2) was associated with creatininemia, eGFR, dialysis, dialysis duration, albuminuria/creatinuria ratio, BMI, biguanide use, DPP4-inhibitor or insulin treatment, the completion of a retinographic check-up within the year, the balance of high blood pressure, magnesemia, HCO3$^-$, CRP, LDL-cholesterol and Hb (Table 4 and Supplementary data, Table S3).

In the multivariate analysis, when dialysis patients were considered, eGFR [odds ratio (OR) 0.98 (0.97; 0.99), P < .0001] was the only variable associated with high podiatric risk. After exclusion of the dialysis patients, eGFR [OR 0.98 (0.97; 0.98), P < .0001] and albuminemia [OR 0.92 (0.87; 0.98), P = .006] remained associated with podiatric risk (Table 5).

eGFR threshold predicting podiatric risk

After ROC analysis, the Youden index best estimating the risk of reaching podiatric stage ≥2 was 45 ± 11 mL/min/1.73 m^2 [area under the curve (AUC) 0.76] for the entire population and 68 ± 6 mL/min/1.73 m^2 (AUC 0.70) after excluding hemodialysis patients (Fig. 3a).

Further, the Youden index best estimating the risk of an error for the 10-g Semmes–Weinstein monofilament test was 46 ± 14 mL/min/1.73 m^2 (AUC 0.62) for the entire population and 76 ± 13 mL/min/1.73 m^2 (AUC 0.59) after excluding hemodialysis patients (Fig. 3b). Results for eGFR levels are presented in the Supplementary data, Table S4.

Sensitivity analysis

In the sensitivity analysis, 106 patients without missing data were analyzed. We found a persistent association between the podiatric risk and the eGFR (β = –0.014 ± 0.003, P < .0001) (Table 6).

DISCUSSION

To our knowledge, this is the first study that highlight a close association between the podiatric risk and eGFR level. Indeed, we found that a low eGFR and worse CKD stage were linked to a greater podiatric risk of DFU. However, we found no association between podiatric risk and diabetes type, duration of diabetes, and HbA1c.

Renal function and risk stage in the overall population

The main result of this study underscored that the podiatric stage progressively increased as eGFR level decreased, especially up to stage 2. This result persisted whether dialysis patients were considered or excluded. The optimal eGFR cut-point in screening for diabetic patients at risk of stage ≥2 in our study was 68 mL/min/1.73 m^2 when patients on dialysis were considered a specific population and excluded from the analysis. A threshold of 60 mL/min/1.73 m^2 was already shown to differentiate in terms of prognosis for people with active foot wounds [7] and cardiovascular outcomes [18]. The high cut-point value of eGFR may be a sign of renal vascular damage before the occurrence of more severe renal impairment. Indeed, arteriolar lesions found on renal biopsies do not correlate well with GFR at the time of the biopsy [19].

Table 2: Clinical and biological characteristics according to podiatric risk.

Variables	Stage 0 (n = 260)	Stage 1 (n = 57)	Stage 2 (n = 72)	Stage 3 (n = 97)	P-value
Age (years)	63.2 (±16.0)	65.6 (±11.0)	66.8 (±14.9)	64.1 (±17.5)	.24
Female (%)	34.6	35.1	34.7	34.0	.94
Diabetes Type 2 (%)	83	86	85	86	.45
Diabetes duration (years)	16.1 (±11.9)	13.8 (±11.1)	14.3 (±11.5)	16.5 (±13.4)	.70
Ischemic heart disease (%)	23.1	26.3	27.8	23.71	.64
High blood pressure (%)					.0001
Not at the target	18.5	19.3	33.3	27.8	
Diabetic treatments					
Insulin (%)	52.5	61.2	53.2	71.1	<.001
Biguanide (%)	36.1	49.1	55.6	43.2	.02
Renal function					
Creatininemia (μmol/L)	102 (±64)	130 (±88)	154 (±81)	148 (±88)	<.0001
eGFR (mL/min/1.73 m^2)	75.3 (±34.8)	56.8 (±33.9)	34.1 (±33.5)	38.8 (±34.1)	<.0001
eGFR level (%)					
>90 mL/min/1.73 m^2	43.4	22.8	8.3	11.3	
60–90 mL/min/1.73 m^2	23.1	21.1	18.1	15.5	
45–60 mL/min/1.73 m^2	10.0	15.8	4.1	13.4	
30–45 mL/min/1.73 m^2	11.5	19.2	16.7	17.5	
15–30 mL/min/1.73 m^2	8.1	8.8	18.1	14.4	
<15 mL/min/1.73 m^2 or dialysis	3.8	12.3	34.7	27.8	
Dialysis (%)	1.9	8.8	29.1	25.8	<.0001
Dialysis duration (days)	204 (78; 960)	486 (387; 568)	1238 (364; 2166)	1590 (861; 2170)	.04
Albuminuria/creatinuria (mg/g)	144 (±419)	395 (±1310)	355 (±794)	790 (±1673)	.003
Biology					
HbA1c (%)	7.7 (±1.6)	7.5 (±1.4)	7.5 (±1.4)	7.6 (±1.4)	.39
HCO3$^-$ (mmol/L)	24.9 (±3.5)	24.9 (±3.2)	23.9 (±3.0)	24.0 (±3.2)	.04
LDL-cholesterol (mmol/L)	2.49 (±0.96)	2.07 (±0.91)	2.48 (±0.83)	1.91 (±0.80)	.001

Data are presented as percentage, mean (±SD) or median (25th; 75th centile).
eGFR: estimated GFR according to CKD-EPI formula.

Table 3: Variables associated with podiatric risk after multivariate analysis, with (Model A) or without (Model B) dialysis patients.

Variables	β	SE	P-value
Model A			
eGFR (mL/min/1.73 m^2)	−0.013	0.0017	<.0001
Albuminemia (g/L)	−0.039	0.014	.007
CRP (mg/L)	0.0059	0.0035	.09
Retinography within the year	0.26	0.15	.09
Model B			
eGFR (mL/min/1.73 m^2)	−0.012	0.0030	<.0001
Albuminuria/creatinuria (mg/g)	0.00016	0.0001	.12
CRP (mg/L)	0.012	0.0057	.03

In any case, we did note an increasingly more significant relationship than previously described in studies focused on DFU [6, 20]. This is further evidence of a joint evolution of the two complications. Moreover, this hypothesis was further reinforced by the association in the univariate analysis between the level of albuminuria (and glomerular damage) and the podiatric stage.

People on dialysis are a high-risk population and they require special attention, but an evaluation before they reach the CKD G5D—i.e. during the nephrological follow-up of the attempt to slow down the renal disease—seems equally important. According to several studies, efforts in dialysis centers have led to tangible improvements in patients' foot health [20–24], but we are not aware of any specific podiatric intervention study during the

follow-up period prior to CKD G5D [8]. Our results may be explained by our focus for the first time on the progressive markers of DFU risk and not on the event that is the ulcer. In this sense, we agree with previous reports on the progressive link between PND and creatininemia [25].

Podiatric stage and CKD G5D

As expected, the patients on dialysis had high podiatric risk stages. However, although 73.6% of those with CKD G5D were in stage 2 or 3, 15.5% were in stage 0 and 9.9% in stage 1. Within this population with CKD G5D, with or without dialysis, it was not clear whether some patients were at greater risk than others. Further study is thus needed to determine whether patients in stage 0 or 1 have been newly diagnosed with diabetes. Indeed, it will be important to follow this population to quantify their actual risk of developing a DFU, especially since according to the IWGDF stratification, all patients on dialysis are automatically classed into stage 3. In any case, the population with CKD G5D was overall in a worse risk stage, although this did not appear to be a specific step in foot complications [6, 20].

Notably, when we focused on dialysis itself, we found that dialysis duration was a strong predictor of worse DFU risk classification. However, given the wide distribution of stages among the patients on dialysis and the small number of them in stage 0 or 1, it seems that hundreds of patients on dialysis would need to be recruited in order to draw statistically significant conclusions. A study of DFU-free survival might be more appropri-

Table 4: Clinical and biological characteristics according to a podiatric risk <2 or ≥2.

Variable	Podologic grade <2 ($n = 317$)	Podologic grade ⩾2 ($n = 169$)	P
Age (years)	63.9 (14.8)	66 (14.8)	.06
Female (%)	34.7	34.3	.9
Diabetes Type 2 (%)	83.3	85.2	.58
Diabetes duration (years)	15.7 (11.8)	15.6 (12.6)	.61
High blood pressure (%)	37.6	23.6	.02
Diabetic treatments			
Insulin (%)	70.7	38.5	<.001
Biguanide (%)	38.5	48.5	.03
Renal function			
Creatininemia (μmol/L)	107 (69)	151 (84.8)	<.0001
eGFR (mL/min/1.73 m^2)	71.9 (35.3)	36.8 (33.9)	<.0001
eGFR stage (mL/min.1.73 m^2)			
>90 mL/min/1.73 m^2	39.7	10	
60–90 mL/min/1.73 m^2	22.7	16.6	
45–60 mL/min/1.73 m^2	11	9.5	
30–45 mL/min/1.73 m^2	12.9	17.2	
15–30 mL/min/1.73 m^2	8.2	16	
<15 mL/min/1.73 m^2 or dialysis	5.4	30.8	
Dialysis (%)	3.2	27.2	<.0001
Dialysis duration (days)	199 (606)	55 (419)	<.0001
Albuminuria/creatinuria (mg/g)	182 (637)	622 (1405)	.0002
Biology			
HbA1c (%)	7.62 (1.52)	7.52 (1.41)	.23
Hb (g/dL)	13.6 (1.8)	12.4 (1.83)	<.0001
HCO3$^-$ (mmol/L)	24.9 (3.4)	24 (3.1)	.009
LDL-cholesterol (mmol/L)	2.33 (0.96)	2.12 (0.85)	.02

Data are presented as percentage, mean (±SD).

Table 5: Significant association with podiatric risk ≥2 after multivariate analysis, with (Model A) or without (Model B) dialysis patients.

Variables	OR	95% CI	P-value
Model A			
eGFR (per 1 mL/min/1.73 m^2)	0.98	0.97–0.99	<.0001
Albuminemia (per 1 g/L)	0.95	0.89–1.01	.10
Model B			
Retinograhy within the year (%)	1.63	0.90–2.96	.11
eGFR (for 1 mL/min/1.73 m^2)	0.98	0.97–0.98	<.0001
Albuminemia (per 1 g/L)	0.92	0.87–0.98	.006

ate in this population to evaluate the impact of the quality of dialysis.

HbA1c, DFU risk stage and renal function

We did not find a correlation between HbA1c and the podiatric stage in this population with a high prevalence of renal failure, but we did find a progressive decrease in HbA1c as eGFR deteriorated, as already described [26]. HbA1c had no impact on the risk stage, whereas intensive insulin therapy showed some impact on PND, retinopathy and nephropathy in diabetes type 1 [27]. This remind us that a glycemic control strategy to prevent DFU must be built over time for optimal results [28, 29] and that intensive glycemic therapy might not necessarily be efficient to prevent DFU once complications have set in. We should note that we were unable to adjust our results on hypoglycemic events or glycemic variability, although it is known that hypoglycemic events and glycemic variability can worsen PND [30–32].

Clinical implications

A foot examination is not part of the nephrologist's usual clinical examination, although significant progress in footcare has been made in dialysis centers. Studies are consistent in showing the effectiveness of therapeutic education or diabetic foot monitoring programs in dialysis centers, notably with regard to predicting wound evolution and even reducing the incidence of amputations [23, 33, 34]. The impact of a systematic podiatrist consultation for eGFR values <60 mL/min/1.73 m^2 should now be investigated.

It was quite surprising and unsettling that we were unable to find a sufficiently strong link to point to a threshold of predictability of a monofilament error. Renal function may in some way interact independently of this monofilament test result, and this possibility also deserves further study.

Limitations and strengths of the study

We recruited only outpatients with stable eGFR and to our knowledge, this is the first description of this type of population using the IWGDF stratification system.

Our prospective study included a recent creatinine blood test and a standardized clinical examination based on the international 2019 IWGDF risk stratification guidelines, which have been recognized by health authorities [17, 35]. Unfortunately, we were not able to define CKD stage 1 and 2 in all patients with an eGFR >60 given the lack of data on the necessary criteria requested by the KDIGO (albuminuria, hematuria and kidney morphology). As we found a rather high threshold of eGFR associated with the podiatric stage, it would be interesting to redo a study to analyze stages 1 and 2.
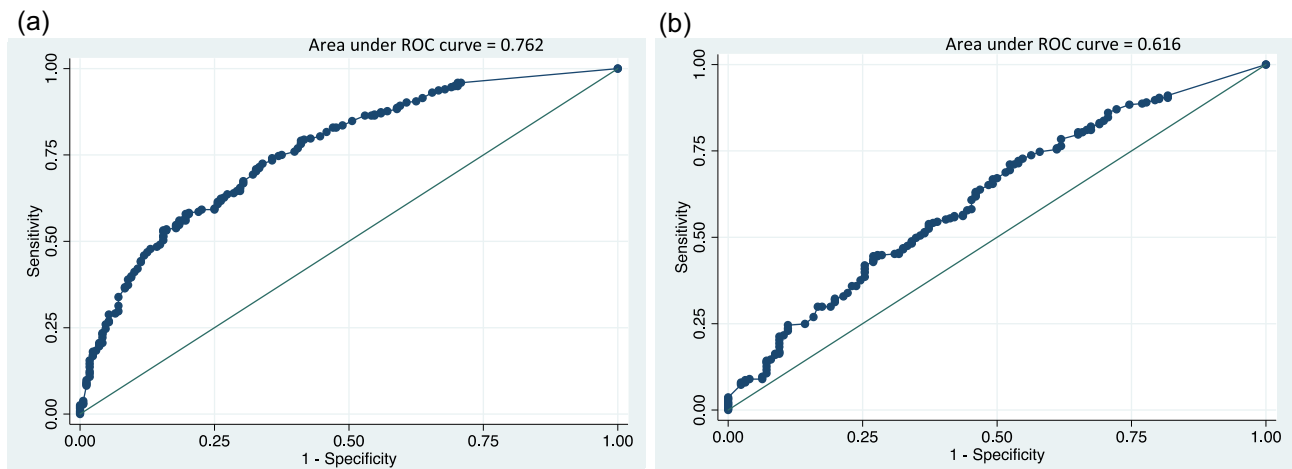
(a)

(b)

Figure 3: ROC analysis showing the predictability of the eGFR on a 2019 IWGDF podiatric stage ≥2 (**a**) and an error at the 10-g Semmes–Weinstein monofilament test (**b**).

Table 6: Variables associated with podiatric risk in the sensitivity analysis.

Variables	β	SE	P-value
eGFR (mL/min/1.73 m^2)	−0.014	0.003	<.0001
Albuminemia (g/L)	−0.055	0.024	.02
CRP (mg/L)	0.012	0.006	.03

We took into account a maximum of biological confounding factors, and 79% of all patients with eGFR <60 mL/min/1.73 m^2 had had a recent phosphocalcic and parathyroid hormone control. These missing data remain a limitation to the study, especially regarding the possibility of integrating them as a correction factor in a multivariate analysis. Although we had set up a systematic recruitment protocol, we had a good distribution of patients across all stages of CKD and with no CKD. Similarly, we recruited the same number of patients in risk stage 0 as in stage 1, 2 or 3. This balanced distribution of the patients of our study may have strengthened the results.

CONCLUSION

Poor renal function is associated with high podiatric risk and patients on dialysis have the higher risk. The effect of renal function decline on podiatric risk seems to appear early, and diabetic patients with CKD should be referred to foot specialist centers to benefit from enhanced education programs and careful foot management. This study reinforces the arguments for joint work between nephrologists and diabetologists.

SUPPLEMENTARY DATA

Supplementary data are available at *ckj* online.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no relevant financial interests.

AUTHORS' CONTRIBUTIONS

Research idea and study design: J.-B.B., I.S., A.S., S.J., A.A.; data acquisition: J.-B.B.; data analysis/interpretation: J.-B.B., I.S., A.S.; statistical analysis: I.S.; supervision or mentorship: I.S., A.S., A.A. Each author contributed important intellectual content during manuscript drafting or revision and agrees to be personally accountable for the individual's own contributions and to ensure that questions pertaining to the accuracy or integrity of any portion of the work, even one in which the author was not directly involved, are appropriately investigated and resolved, including with documentation in the literature if appropriate.

DATA AVAILABILITY STATEMENT

The data underlying this article will be shared on reasonable request to the corresponding author.

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