Original Article

Prevalence and Risk Factor of Diabetic Foot Syndrome in Diabetic Kidney Patients

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Objective: Study the prevalence of diabetic foot disease in those with concurrent renal disease and evaluate risk factor of developing DFS in consecutive patients with type 1 or 2 diabetes and DKD attending the clinics between 2014 and 2016.

Materials and Methods: Three hundred eighty-four patients were included in the study. Estimated and glomerular filtration rate [eGFR] were calculated according to CKD-EPI. The patients were grouped into chronic kidney disease [CKD], according to eGFR, as stage 3, 4, or 5, and were classified as either receiving dialysis therapy or not. The foot assessment included diabetic peripheral neuropathy, peripheral arterial disease, foot ulceration, ankle-brachial index [ABI], and amputation. Risk factors for prevalent foot ulceration were assessed by logistic regression.

Results: Three hundred eighty-four patients with diabetes and DKD (mean age 63 years: male 41%, female 59%) had type 1 and 2 diabetes staging of DKD performed by urine albumin. Stage 3 was 39.25%, stage 4 was 6.75%, and stage 5 was 4.75%. This compared to the non-DKD patients that had higher prevalence of DFS at 46.6%, diabetic neuropathy 97.7%, impaired ABI (<0.9) 1.1%, prevalent foot ulceration 5.02%, and intermittent claudication 3.3%. There was a significant negative correlation between eGFR and presence of DFS patients with diabetes (adjusted odd ratio 0.992, $p<0.05$). Multiple logistic regression analysis revealed a significant association between the presence of skin infection/discharge and DKD stage 4 (odd ratio 3.33, $p<0.005$). In univariate analysis, the DFS was related to dialysis treatment, smoking, decline of renal function, high HbA1C, and level of albuminuria.

Conclusion: Poor control of diabetes, dialysis, the degree of renal function impairment, and level of urine albumin were independently associated with DFS. Therefore, early screening and intensive foot care should be highlighted in the DKD.

Keywords: Diabetic kidney disease, Diabetic foot syndrome, Dialysis, Albuminuria

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Diabetes is the most common cause of renal disease resulting in the need for renal replacement therapy in Thailand and responsible for 40% to 47% of incidences for renal replacement therapy. The major aetiological factor for renal disease in diabetes is the diabetic microvascular complication of nephropathy[1]. There is much higher incidence of diabetic foot disease in those with concurrent renal disease and the outcome, including amputation and mortality are generally poorer. The major risk factor for foot disease (diabetic foot syndrome [DFS]) in those patients with diabetes and renal disease is peripheral neuropathy, peripheral artery disease [PAD], susceptibility to infection, dialysis therapy, and anemia.

DFS is defined as one or more manifestation of diabetic foot ulcer[2], peripheral neuropathy, infection, intermittent claudication, PAD. Lower extremity amputation is common in patients with the diabetic kidney disease [DKD], and its prevalence is a serious problem for diabetic patients, which also result in higher mortality. It is also well established that diabetes is a major cause of the development of foot lesions, about 25% of patients with diabetes develop foot ulceration as a complication during their lifetime[2]. On entering renal replacement programs, about 10% of patients already have a history of a lower extremity amputation[3] and while on dialysis, approximately 4% of patients require an amputation each year. The risk of lower extremity amputation in a diabetic patient with end-stage renal disease [ESRD] and uremia is 10 times higher than that of a diabetic patient without uremia. The pathways to foot ulceration are multifunctional and involve the combinations of physiological, mechanical, self, and treatment factors. Diabetic nephropathy has been identified to be an important risk factor for foot ulceration and amputation[4]. Retrospective studies in patients with diabetes have shown that the incidence of foot ulceration increases with a progressive renal

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impairment[5]. The highest incidence of foot disease is also seen across all categories of renal disease, chronic kidney disease [CKD] stage 3 and 4[5], the patients receiving hemodialysis, and the patients treated with renal transplantation[6,7]. One risk factor for foot disease in those with diabetes and renal disease is PAD. Relative risk of incident PAD is defined as the ankle-brachial index [ABI] of less than 0.9, new intermittent claudication, absent pedal pulse in patients with CKD, estimated glomerular filtration rate [eGFR] of 15 to 59 ml per minute per 1.73 m^2, compared to those with normal kidney function when adjusted for age, gender, race and cardiovascular disease risk factors. Uremia compromises many aspects of mechanisms of defense, and causes susceptibility to infection by pathogenic organism[8]. Infected foot ulcer in those with renal disease is also more likely to harbor resistant microorganism. The risk factor is dialysis therapy, which recently has been shown to predict foot ulceration independently with potential confounders such as neuropathy, peripheral vascular disease, foot scab care measures, and ethnicity. Anemia, a common complication of CKD, is also associated with a poor tissue oxygenation and impaired wound healing.

The data are surprisingly limited on possible correlation between diabetic foot complication and renal dysfunction in a diabetes patient. The authors had seen the association between the degree of renal function[6] impairment and DFS, including the risk factor that could cause a higher incidence of amputation.

Materials and Methods

Patients

A retrospective cross-sectional study was performed to identify the potential association between DFS and renal function in patients with DKD at the Taksin Hospital in Bangkok metropolitan, Thailand. The Patient's data were stored between 2014 and 2016. Three hundred eighty-four stable diabetes type 1 and type 2 with DKD patients were investigated in the diabetic and nephrology clinic. They were classified as either receiving dialysis therapy (dialysis) or not (no dialysis). A Risk factor for the prevalent foot ulceration was accessed by multiple logistic regressions. Exclusion criteria were the patients who developed serious systemic illness, pregnancy, low extremity amputated, and age under 18 years.

Method

Classification of DKD, according to the Kidney Disease, Improving Global Outcomes 2012 Guideline[9,10] was done. The eGFR was calculated according to the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] equation formula. The patients were grouped into the CKD stage, according to eGFR, and presence of albuminuria[9]. The study population consisted of 384 adult patients between the ages of 18 and 76 years. From previous study, the prevalence of DFS in diabetic kidney patients was 10%[3]. All the patients had foot examinations included peripheral neuropathy, intermittent claudication, prior foot ulceration, skin infection, discharge, ABI, peripheral arterial disease, and pedal pulse. In the present study entry, the age, duration of diabetes, body mass index, weight (kilogram), blood pressure, dialysis, and smoking rate were assessed. The patients record included hemoglobin A1C [HbA1C], serum creatinine (mg/dl), eGFR (mg/ml/1.73 m^2), and urine albumin level, which was determined in the first morning through their urine sample. The diabetic peripheral neuropathy was assessed by the clinical examination using 10 g monofilament (Semmes-Weinstein monofilament) at first, third, and fifth metatarsal head and plantar of both feet. It was enough to identify individuals at risk of ulceration[11-15]. Peripheral arterial disease was assessed through palpation of dorsalis pedis pulse bilaterally and determination of ABI using a doppler ultrasound probe in both legs. PAD was defined as at least one of the following, ABI smaller than 0.9, claudication, or absence of one or more pedal pulses on palpation done by a well trained nurse at foot center. Claudication is usually referring to impairment in walking or pain, discomfort as tiredness in the legs that occurs during walking or standing and relieved by rest. Non-invasive studies were performed to determine lower extremity perfusion. The major amputations were defined as amputations proximal to the ankle joint.

Statistical analysis

Sample size was determined to demonstrate prevalence of DFS in diabetic kidney patients using a significance level of 5% and a two-side test. Assuming the prevalence of DFS of 10%[3], 384 evaluable diabetic kidney patients were needed to achieve a power of 95%. For descriptive statistical analysis, the mean, standard deviation, and absolute frequency were calculated. Statistical analysis was performed with a t-test to compare the variable parameter between the groups, Pearson Chi-square and Fisher's exact test were performed for the categorical date (DFS yes/no and

eGFR). The 95% confidence interval for the properties and percentages were estimated using the Modified Wald Formula. For estimating possible relationships of eGFR with DFS (yes versus no) as the dependent variable and eGFR increase as an independent variable, multiple logistic regression analysis was used to test the correlation between the two variables. The multivariable models were adjusted for systolic blood pressure, diastolic blood pressure, duration of diabetes, mean adjusted, HbA1C, body mass index, level of urine albumin, age, and anemia (Hb <10 g/dl). The risk estimates were presented as odds ratios and 95% confidence interval. A *p*-value smaller than 0.05 was considered to be statistically significant. All the statistical analysis was performed using SPSS for windows version 13.

Results

This investigation was a single centre retrospective cohort study in Taksin Hospital. Three hundred eighty-four stable diabetes patients, with a mean age of 63±13 years, (range 27 to 91 years) and 59% female, 41% male were enrolled in the present study. All patients with albuminuria (greater than 30 mg/dl) were studied according to the eGFR in the CKD stages as defined by the kidney disease outcomes quality initiative.

The data of baseline characteristic are presented in Table 1. One hundred seventy-nine patients (46%) had an active or a history of DFS. However, more patients with DFS were found in the higher CKD stage (Figure 1). Only 18 dialysis patients were included. Fourteen patients were treated with hemodialysis and the remaining were treated with peritoneal dialysis. The authors' study of greater CKD proportion had DFS.

Among these patients, 37% had hypertension and 28.6% had history of smoking. The mean body mass index was 28.9, and 7.5% of these patients had hemoglobin level of 10 g/dl or less.

From 176 patients, 44% of the patients had peripheral neuropathy. None had prior lower limb amputation, 5.02% of foot problems were foot ulcers. The number of clinical manifestations of diabetic foot problems is defined in Table 2.

The authors measured DFS manifestation in 179 patients and observed a level of correlation to a diabetic foot ulcer. Both the skin infections discharge and CKD stage 4 had shown to cause most diabetic foot ulcer problems. The present study had a small number of chronic kidney stage 5 (Table 3).

Comparison between the patients without DFS and those with DFS revealed that diabetic patients with DFS had significant albuminuria, anemia, and higher HbA1C. Smoking and dialysis have significantly influenced the prevalence of DFS.

The Multivariate logistic regression analysis revealed a significant negative association between the change in eGFR and DFS (Table 4). Poor glycemic control diabetes (adjusted odd ratio 1.15, $p<0.05$) and the level of urine albumin (adjusted odd ratio 1.00,

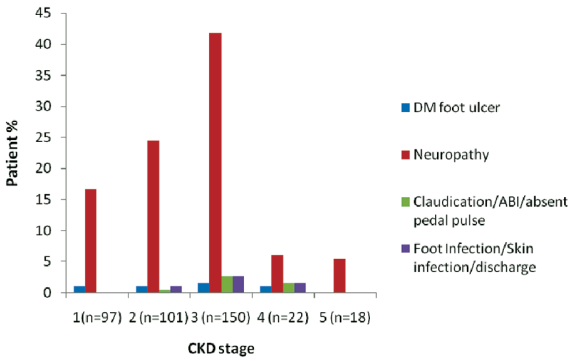

Figure 1. Patients with higher stage 5 of chronic kidney disease had the diabetic foot syndrome more often.

Table 1. Baseline characteristics of patients with diabetic kidney disease

Characteristics	Total (n = 384)
Age (year), mean ± SD	63±13
Gender: male (%)	41.0
Body mass index, mean ± SD	28.9±3.05
Dialysis:non-dialysis, n	18:368
Duration of diabetes (year), mean ± SD	10.54±8.3
Hypertension (%)	37.0
Blood pressure (systolic/diastolic) (mmHg), mean ± SD (min-max)	135±19/73±11 (91 to 199/42 to 107)
Smoking (%)	28.6
Serum creatinine (mg/dl), median (range)	1.16 (0.35 to 8.65)
HbA1C, mean ± SD (min-max)	7.59±2.32 (4 to 26.4)
Hb <10 (%)	7.5

Table 2. Foot problem in diabetic patients with DFS in concurrent studies

Subjects	Number (n = 179), n (%)
Neuropathy	175 (97.7)
Ankle brachial index <0.9	2 (1.11)
Absent pedal pulses	1 (0.55)
Intermittent claudication	6 (3.3)
Current ulcer	9 (5.02)
Skin infection	2 (1.11)
Discharge	2 (1.11)

DFS = diabetic foot syndrome

$p<0.05$) were also positively correlated with DFS.

Discussion

Diabetes is one significant non-communicable disease that is increasing in the world and in Thailand. The national statistical office's data, numbers of inpatients from Thai Health Service units of the whole diabetes rose from 213,136 (in 2003) to 508,753 (in 2012). The complication of diabetes can be categorized into two types, microvascular and macrovascular diseases. One of the major macrovascular complication is the DFS and microvascular complication is the diabetic nephropathy[5].

Foot complication is common in patients with diabetes, however, CKD is an independent risk factor for the development of foot lesions in the diabetic population. Lower extremity amputation has a high mortality and leaves more patients unable to perform the activity of daily living. The authors demonstrated a close association between the DKD and DFS. Correlation analysis also showed a significant reverse relationship between eGFR and DFS. Metabolic control as measured by adjusted HbA1C value is worse in diabetes with DFS because prolonged hyperglycemia increases the risk of infection. Uremia itself causes significant immune dysregulation that reduces the ability of the body to defend against infection. Patients with DFS have a high prevalence, smoking history, older, dialysis, and higher HbA1C. The prevalence of a higher albuminuria was statistically significant in the patients with the presence of DFS. In general, the level of albuminuria predicts progression of DKD. The more albumin in the urine, the greater progressive renal function loss. Albuminuria is classified into two types, microalbuminuria (albumin creatinine ratio 30 to 300 mg/g) and macroalbuminuria (albumin creatinine ratio greater than 300 mg/g). In this study, urine albumin was also associated with DFS. Other parameters such as duration of diabetes, hypertension, body mass index, did not modify the relationship between eGFR and DFS, in contrast to previous studies. Multiple logistic regression has been used.

There is very little data regarding to the relationship between DFS and DKD in Thailand. In a previous study, Wolf et al retrospectively analysed data from individuals with diabetes showing a strong association between the severity of CKD and the onset of DFS[6]. The CKD stages were calculated in the study based on eGFR, including data on albuminuria. Therefore, the author added to the existing evidence that neuropathy is a risk factor for DFS. Neuropathy is the primary cause of foot ulceration in diabetes. The motor component of peripheral neuropathy leads to foot denervation, which results in a marked increase in pressure conducted through the plantar aspects of metatarsal hand, toes, and heels. The ongoing weight-bearing due to lack

Table 3. Biochemical and parameter between DFS and non DFS

Parameter	DFS (n = 179)	Non DFS (n = 221)
Age (year), mean ± SD	65.62±11.8*	61±12.67
Body mass index, mean ± SD	27.5±6.04	27.5±9.42
Dialysis:nondialysis, n	10:169**	8:213
Duration of diabetes, mean ± SD	11.62±8.09	10.45±9.59
Hypertension, mean ± SD		
Systolic blood pressure	138±20.39	133±20.39
Diastolic blood pressure	73±11.8	72±12.07
Smoking (%)	9.4**	8.0
eGFR, mean ± SD	58.53±27.4	68±32
Hb <10 (%)	10.0	5.4
Hemoglobin A1C, mean ± SD	8.08±1.78**	7.17±2.19
Urine microalbumin, mean ± SD	726.7±185**	229.86±78.236

DFS = diabetic foot syndrome; eGFR = estimated glomerular filtration rate

* $p<0.05$ versus no DFS, ** $p<0.005$ versus no DFS

Table 4. Multivariate regression analysis for diabetes and DFS (yes/no) as dependent value

Indicator	Regression coefficient	Standard error	Adjusted odd ratio	95% confidence interval	*p*-value
GFR	-0.008	0.004	0.992	0.967 to 0.998	0.037
Age	0.033	0.019	1.034	0.997 to 1.072	0.074
Systolic blood pressure	0.003	0.013	1.003	0.978 to 1.029	0.803
Diastolic blood pressure	0.014	0.021	1.014	0.974 to 1.056	0.502
HbA1C	0.141	0.052	1.151	1.048 to 1.614	0.007
Urine microalbumin	0.0001	0.000	1.000	1.000 to 1.001	0.015
Body mass index	0.002	0.038	1.002	0.930 to 1.081	0.953
Duration of diabetic	-0.003	0.026	0.997	0.948 to 1.048	0.905
Smoking	-0.349	0.383	0.705	0.496 to 5.493	0.362

GFR = glomerular filtration rate

of pain inhibits the normal healing process so that lesions tend to enlarge and with chronicity develop an infection. Autonomic neuropathy was seen in patients with diabetes and CKD, reducing perfusion across capillary beds and resulting in microvascular insufficiency, which further compromises healing. Autonomic neuropathy also results in dry fissured skin, commonly seen in a patient with renal disease. Ndip et al reported that patients with diabetic foot ulcers were fivefold higher in dialysis-treated patients than in pre-dialysis patients with adjustment for the potential confounders (neuropathy and peripheral arterial disease)[7].

Diabetic foot ulcer, as classified by Wagner, are correlated with eGFR and dialysis. The author cannot prove that high level of albuminuria is a pathophysiological mechanism. Advanced glycation end products have been implicated in diabetic complication and their concentrations are increased in DKD. Podocytes express specific receptors for age and binding to these receptors podocyte pathology including induction proteinuria. The process of wound healing is a dynamic and complex process that involves the process of inflammation, caused by aging. The impairment of wound healing is a major feature of DFS.

Apart from this, chronic inflammation is also thought to play an important role in the development of atherosclerosis, and the incidence of clinical peripheral arterial disease[9].

Another frequently described risk factor for diabetic foot ulcer is chronic hyperglycemia. Inadequate glycemic controls are associated with poor complication in diabetes including microvascular and macrovascular outcomes. The result of the diabetes control and complication trial [DCCT] and the United kingdom prospective diabetes study [UKPDS][17,18] support the long-held theory that chronic poor control of diabetes is associated with systemic illness such as DFS, a complication and progression of diabetic nephropathy. It compromises many aspects of the mechanism of defense against the infection, thus have a higher proportion of infected foot ulcer. Dialysis patients may result in subjects neglecting other aspects of their care, such as foot care. This also causes depression affecting attendance caused by uremia.

The present study correlated among DFS, eGFR, urine albumin, and HbA1C as shown in the equation below. The objective of the author was to determine the risk predictor of DFS among DKD patients. A score of this equation of more than 10 is associated with the greatest opportunity to DFS.

DFS = 0.992 GFR + 1.15 HbA1C + 1 albuminuria

There are some limitations in the present retrospective study, including the limit of some relevant data, selection bias, and unknown date of intiate smoking habits and dialysis.

The present findings have important clinical implication as they alert health care practitioner that high score of DFS equation and dialysis is an independent risk factor for foot ulceration, thus requiring extra vigilance and foot care. This support that patients due to more decline renal function, or receiving dialysis should have intensive education, including the initiation of measures to prevent foot ulceration.

Diabetic patients with CKD are considered as a high risk group for DFS. Therefore, they should be regularly screened for DFS during each visit. Most dialysis centers should make screening protocols for early detection of this DFS. Foot care program emphasizing preventive management can reduce the incidence of foot ulcerlation through modification of self-care practice, appropriate evaluation of risk factors, foot hygiene care, and early treatment of new or impending lesions. Therefore, long term studies are still needed to further reduce limb amputation.

What is already known on this topic?

There is much higher incidence of diabetic foot disease in those with concurrent renal disease and outcome, outside Thailand. The major risk factors for foot disease (DFS) in those patients with diabetes and renal disease are peripheral neuropathy, PAD, and susceptibility to infection.

What this study adds?

Independent relative risk to diabetic foot ulcer stratified by eGFR by Cox proportional hazard model (multivariate analysis) in Table 5 has not been shown in previous study and is making a new screening criteria in DKD.

In present's analysis revealed a significant negative association between the change in eGFR and DFS (Table 4). Poor glycemic control diabetes and the level of urine albumin were also positively correlated with DFS, which was not shown in previous studies.

The correlation among DFS, eGFR, urine albumin, and HbA1C shown in the equation below, helps determine the risk predictor of DFS among DKD patients. The findings show that a score higher than 10 is associated with the greatest risk to DFS.

DFS = -0.992 GFR + 1.151 HbA1C + 1 albuminuria

Table 5. Independent relative risk to diabetic foot ulcer stratified by eGFR by Cox proportional hazard model (multivariate analysis)

Diabetic kidney disease stage		Skin infection/ discharge	Peripheral artery disease/absent pedal pulse/Intermittent claudication	Neuropathy
1	>90	No data	No data	1.01[#]
2	60 to 89	0.93[$]	1.06[#]	0.98[$]
3	30 to 59	1.36[+]	1.05[#]	1.01[#]
4	16 to 29	3.33*	0.66[$]	1.02[#]
5	<15	No data	No data	1.11[+]

eGFR = estimated glomerular filtration rate

* Very high risk (relative risk >3), [+] High risk (1.1 to 1.3), [#] Moderate risk (1 to 1.1), [$] Low risk (<1)

This equation predicts threat to diabetic foot ulcer and make new secondary prevention for further lower extremity amputation in the future.

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Potential conflicts of interest

The authors declare no conflict of interest.

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