Study the Correlation between Diabetic Foot Syndrome and the Level of Renal Impairment in Patients with Type II Diabetes among Egyptian Population

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Abstract

Background: Diabetes can lead to a number of serious consequences, including diabetic nephropathy and diabetic foot syndrome (DFS). **Patients and method:** A cross-sectional cohort study in a single tertiary university hospital for a collective of patients with type 2 diabetes was performed. A total of 100 patients with type 2 diabetes were studied, for whom standardized foot examination, fundus examination, L.L. arterial duplex were performed. HbA1c, albuminuria, serum creatinine and blood urea were analysed. Estimated GFR was calculated according to CKD-EPI equation. Patients were classified into phases of chronic kidney disease (CKD) according to their estimated glomerular filtration rate (eGFR) and the occurrence of albuminuria. DFS was classified according to Wagner as well as University of Texas stages. **Results:** There was a significant negative correlation between the Wagner stages and eGFR (P<0.001) as well as University of Texas stages and eGFR (P<0.001) in all patients with type 2 diabetes and DFS (Spearman test). Type 2 diabetes patients with chronic L.L. ischemia had significantly higher HbA1c (P<0.05), higher serum creatinine (P<0.001), higher blood urea (P<0.001), higher A/C ratio (P<0.001) and significantly lower eGFR (P<0.001). **Conclusion:** It is advised that diabetic patients with renal insufficiency undergo more frequent examinations to check for the existence of DFS and should be given specific care and should be educated regarding foot care since there was a significant correlation between the level of impaired renal function and DFS in type 2 diabetic patients who had pre-terminal renal insufficiency.

Key Words: Diabetic nephropathy and diabetic foot syndrome; renal insufficiency; Wagner and University of Texas stages.

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Introduction:

Diabetes mellitus is a chronic metabolic condition that frequently causes pathologic changes in the integumentary, nervous, skeletal, and peripheral vascular systems. Because it is the extension of the body that is typically neglected, the most neglected, and the furthest from the heart, the foot is the first part of the body to show the negative effects of diabetes. Most often, the foot will show the most serious complications, which, if untreated, could lead to death or amputation. (1)

Diabetic nephropathy is the leading cause of the end-stage renal disease. More than 30% of patients with diabetes mellitus develop clinically evident diabetic nephropathy 10–20 years from the onset of disease. (2)

Diabetic nephropathy occurs as a consequence of the interaction between metabolic and hemodynamic factors. It is characterized as glomerulosclerosis and the major morphologic abnormality in Diabetic nephropathy is the thickening of the glomerular basement membrane (GBM) and the expansion of the mesangium. (2) The natural history of type 1 and type 2diabetic nephropathy is similar with regard to the progression from microalbuminuria to proteinuria. (3)

The microvascular lesion of the kidney in diabete mellitus variably been described to generation of advanced glycation end products (AGE) , accumulation of sorbitol , activation of protein kinase C (PKC) and activation of the hexosamone pathway.

Diabetes mellitus is a disease of complications and Diabetic Foot Syndrome is an important problem confronting society and health professionals. (4)

The International Working Group on Diabetic Foot and the World Health Organisation (WHO) describe diabetic foot syndrome to be the foot of diabetic patients with ulceration, infection, and/or destruction of the deep tissues that is also linked to neurological abnormalities and various degrees of peripheral vascular disease in the lower limb.

Diabetes affects at least 120 million individuals around the world, and up to 10% of those people will suffer foot ulceration at some point in their lives; around 9% of national health care costs are spent on diabetes-related issues, almost halve of this is for hospitalization for complications, particularly of the diabetic foot. Throughout the developed world healthcare costs are incurred, but in the developing nations the scarcity of care means that most of the cost is social.

those with diabetes mellitus and concomitant renal disease have a significantly higher risk of mismanaging foot lesions than those without these conditions. They are generally, but not always, regarded a minor clinical concern, despite the fact that they frequently have an effect on the patient's chance of survival. (5)

Diabetes can lead to a number of serious consequences, including diabetic nephropathy and diabetic foot syndrome (DFS). Surprisingly, there is a paucity of information about the possible connection between renal function and the progression of DFS in individuals who have preterminal renal insufficiency. (6)

To study if there is association between the degree of renal insufficiency and diabetic foot syndrome in patients with type 2 diabetes mellitus and renal insufficiency among the Egyptian population?

SUBJECTS AND METHODS

This cross-sectional study was performed to identify a potential association between DFS and renal function in patients with type 2 diabetes in Bani-Suef University Hospital. A total of 100 patients with type 2 diabetes were investigated and had a standardized foot examination.

Inclusion criteria: Patients with type 2 diabetes and any stage of diabetic nephropathy and normal liver and cardiac examination.

Exclusion criteria: Patients with type 1 diabetes, patients with CRF on regular hemodialysis, liver disease, organ failure like cardiac failure, known diagnosis of previous neurological disease causing neuropathy, drug abuse like cocaine abuse and patients with urinary sediment findings suggesting glomerulonephritis (e.g. hematuria, acanthocytes,.....etc), or patients with urinary tract infection.

Patients were screened in the outpatient clinic. All patients studied had established DM using ADA criteria and classified as either type 1 or type 2 and only type 2 patients are included in the study.

All patients are subjected to: Full history taking, including age, sex, duration of diabetes and history of previous diabetic foot ulcers, thorough clinical examination, standardized foot examination, random blood glucose, HbA1c, serum creatinine

level, blood urea level, albumin / Creatinine ratio for albuminuria, estimated glomerular filtration rate(eGFR), which was detected from the CKD-EPI equation, bilateral lower limb arterial duplex and fundus examination to detect retinopathy.

Statistical analysis:

Data were collected, coded and analysed using SPSS software version 17 under windows Vista, Descriptive analysis were performed followed by inferential statistical analysis, and a level of significance of 0.05 was considered. The following tests of significance were applied: Spearman correlation, Chi-Square test, and ANOVA test and student t-test.

RESULTS

This cross-sectional study was conducted on 100 patients with type 2 diabetes, selected from internal medicine outpatient clinic at Bani-Suef University Hospital. Both sexes (54% Females, 46% Males) were enrolled in the study. A standardized evaluation of the foot status was done for all patients and accordingly, patients were categorized into 2 groups: Group (A): Has active or history of DFS. Group (B): Has no DFS.

Table (1): Comparison between patients with DFS and those without DFS according to the following parameters:

Parameter	Group	N	Mean	Std. Deviation	p. value	Sig.
Age(years)	DFS	36	62.7838	9.30691	.001	HS
	No DFS	64	56.1905	9.36682		
Duration of diabetes(years)	DFS	36	16.5833	9.11318	.000	HS
	No DFS	64	6.8636	5.68580		
Systolic blood pressure	DFS	36	168.3784	20.20912	.000	HS
	No DFS	64	136.9841	29.27263		
Diastolic blood pressure	DFS	36	100.0000	9.71825	.000	HS
	No DFS	64	83.6508	14.84344		
Random blood glucose(mg/dl)	DFS	36	246.4595	63.29235	.045	S
	No DFS	64	218.8571	66.89734		
HbA1c(%)	DFS	36	7.9703	1.45771	.007	S
	No DFS	64	7.0000	1.80546		
Blood urea(mg/dl)	DFS	36	71.0000	35.28220	.000	HS
	No DFS	64	40.9524	19.19713		
Serum creatinine(mg/dl)	DFS	36	2.3811	1.51746	.000	HS
	No DFS	64	1.1952	.63460		
Albumin/creatinine ratio	DFS	37	523.0000	264.59035	.000	HS
	No DFS	63	213.4444	199.26379		
eGFR	DFS	36	33.5676	17.79910	.000	HS
	No DFS	64	67.5556	29.10924		

Sig.: Significance; NS: Non-significant (P-value> 0.05); S : Significant (P-value<0.05); HS: Highly significant (P-value<0.01)

A total of 36 patients (36%) from the type 2 diabetes patients have active or history of DFS (Table 1). Compared to type 2 diabetic patients without DFS, those with DFS were significantly older (P<0.005), had longer duration of diabetes (P<0.001), higher systolic blood pressure (P<0.001), higher diastolic blood pressure (P<0.001), higher HbA1c levels (P<0.05), higher serum creatinine (P<0.001), higher albumin/creatinine ratio (P<0.001), lower eGFR (P<0.001).

Table (2): Analysis of Wagner grades of diabetic foot in relationship to the following parameters:

		N	Mean	Std. Deviation	Minimum	maximum	P-value	Sig.
Serum creatinine(mg/dl)	Grade I	13	1.5154	.38481	.70	2.10		
	Grade II	12	2.2538	.71018	.90	3.50		
	Grade III	6	2.7500	.32711	2.40	3.20	0.002	HS
	Grade IV	3	4.4333	2.19393	2.70	6.90	(<0.01)	
	Grade V	2	4.6500	5.58614	.70	8.60		
	Total	36	2.3811	1.51746	.70	8.60		
HbA1c (%)	Grade I	13	7.9308	1.59289	5.20	11.00		
	Grade II	12	7.7308	1.71871	5.00	11.80		
	Grade III	6	8.1833	.86120	7.00	9.10	0.811	NS
	Grade IV	3	8.0000	.91652	7.00	8.80	(>0.05)	
	Grade V	2	9.1000	1.27279	8.20	10.00		
	Total	36	7.9703	1.45771	5.00	11.80		
Albumin/Creatinine Ratio	Grade I	13	415.3846	170.15754	30.00	538.00		
	Grade II	12	465.4615	198.50886	100.00	660.00		
	Grade III	6	665.0000	229.60314	200.00	790.00	0.021	S
	Grade IV	3	893.3333	67.06216	828.00	962.00	(<0.05)	
	Grade V	2	615.0000	827.31493	30.00	1200.00		
	Total	36	523.0000	264.59035	30.00	1200.00		
eGFR	Grade I	13	49.9231	15.51054	37.00	86.00		
	Grade II	12	29.3846	12.78370	14.00	67.00		
	Grade III	6	22.1667	1.72240	20.00	25.00	0.000	HS
	Grade IV	3	13.6667	5.03322	9.00	19.00	(<0.01)	
	Grade V	2	18.5000	19.09188	5.00	32.00		
	Total	36	33.5676	17.79910	5.00	86.00		

Sig.: Significance NS: Non-significant (P-value 0.05)
S: Significant (P-value<0.05) HS: Highly significant (P-value<0.01)

Table 2 shows that the eGFR significantly decreased (P<0.001) and A/C ratio significantly increased (P<0.001) with increasing Wagner stages.

Table 3 shows that the eGFR significantly decreased (P<0.005) with increasing University Of Texas stages.

Table 4 shows a significant positive correlation between the Wagner stages and A/C ratio (P < 0.001) and a significant negative correlation between the Wagner stages and eGFR (P < 0.001) in all patients with type 2 diabetes.

DISCUSSION

In diabetic feet, both macrovascular complications and microvascular complications (neuropathy) play important rolesMonnier et al. were the first to describe the connection between the buildup of AGE in skin collagen and the severity of long-term problems caused by microvascular diabetes. (7)

In a significant number of people who have type 2 diabetes, our research uncovered a strong connection between renal function and DFS. The examination of correlation also demonstrated a significant reverse link between eGFR and the Wagner as well as the Armstrong stages of DFS. This confirmed that patients with a lower eGFR have more severe stages of DFS than those with a higher eGFR. When measured by HbA1c levels, metabolic management in type 2 diabetics with DFS was found to be poorer. In contrast to a recent

cross-sectional study in Germany that looked at DFS at the primary care level, our findings contradicted those of the study. Only a change of 10 milliliters per minute in eGFR was found to be a significant independent predictor by multiple regression analysis, whilst the other parameters showed no significant association. In contrast, a change of 10 milliliters per minute in diastolic blood pressure, duration of diabetes, and diastolic blood pressure were strongly linked with the occurrence of diabetic foot syndrome in type 2 diabetes.

Table (3): Analysis of University of Texas grades of diabetic foot in relationship to the following parameters:

		N	Mean	Std. Deviation	Minimum	Maximum	P-value	Sig.
Serum creatinine(mg/dl)	Grade I-A	4	1.7000	.00547	1.60	1.80		
	Grade I-B	7	1.4875	.43569	.70	2.10		
	Grade I-D	1	1.0000	-	1.00	1.00		
	Grade II-A	3	1.8333	.23094	1.70	2.10		
	Grade II-B	7	2.5857	.66940	1.80	3.50	0.119	NS
	Grade II-C	1	2.6000	-	2.60	2.60	(>0.05)	
	Grade II-D	2	1.5500	.91924	.90	2.20		
	Grade III-B	3	2.8333	.40415	2.40	3.20		
	Grade III-C	1	3.0000	-	3.00	3.00		
	Grade III-D	7	3.9429	2.79037	.70	8.60		
	Total	36	2.3811	1.51746	.70	8.60		
HbA1c (%)	Grade I-A	4	8.1000	1.19164	6.80	9.50		
	Grade I-B	7	8.0875	1.77879	5.20	11.00		
	Grade I-D	1	6.0000	-	6.00	6.00		
	Grade II-A	3	7.5667	1.07858	6.80	8.80		
	Grade II-B	7	6.9714	1.34996	5.00	8.50	0.269	NS
	Grade II-C	1	8.6000	-	8.60	8.60	(>0.05)	
	Grade II-D	2	10.200	2.26274	8.60	11.80		
	Grade III-B	3	0	.90000	7.30	9.10		
	Grade III-C	1	8.2000	-	8.90	8.90		
	Grade III-D	7	8.9000	1.05017	7.00	10.00		
	Total	36	8.2571	1.45771	5.00	11.80		
			7.9703					
A/C Ratio	Grade I-A	4	451.00	32.10400	420.00	490.00		
	Grade I-B	7	00	172.0930	30.00	538.00		
	Grade I-D	1	442.00	0	60.00	60.00		
	Grade II-A	3	00	-	544.00	550.00		
	Grade II-B	7	60.000	3.05505	180.00	610.00	0.121	NS
	Grade II-C	1	0	202.3814	632.00	632.00	(>0.05)	
	Grade II-D	2	546.66	2	100.00	660.00		
	Grade III-B	3	67	-	200.00	733.00		
	Grade III-C	1	431.28	395.9798	757.00	757.00		
	Grade III-D	7	57	0	30.00	1200.00		
	Total	36	632.00	304.0444	30.00	1200.00		
			00	0				
			380.00	-				
			00	362.0541				
			551.00	9				
			00	264.5903				
			757.00	5				
			00					
			784.28					
			57					
			523.00					
			00					
eGFR	Grade I-A	4	44.250	2.50000	41.00	47.00		
	Grade I-B	7	0	19.33908	37.00	86.00		

Table (4): Nonparametric correlation between Wagner grades of DFS and both Albumin/Creatinine Ratio and eGFR:

			A/C Ratio	eGFR
Spearman's rho	Wagner grade	Correlation Coefficient	0.566	-0.810
		P- Value	0.000	0.000
		N	36	36

There are unexpectedly very few data about the relationship between DSF and CKD in diabetic patients, and the majority of studies have only looked at dialysis patients. Even though every practising clinician may feel that patients with CKD are more likely to have DFS, there is shockingly little research on this topic. (8) The majority of these research suggest that CKD is linked to peripheral artery disease rather than death from cardiovascular causes (DFS). (9(Margolis and coworkers recently conducted a retrospective analysis of data collected by doctors in the UK who are part of the Health Information Network (THIN) and who have treated patients with diabetes. (10) The results of this big study corroborate our own findings of a robust link between CKD severity and the beginning of DFS, and they also reveal that this relationship is observed even in patients with less severe CKD stages.

A buildup of AGEs in the kidney may, in both humans and rodents, be a factor in the progressive alteration of renal architecture and decreased renal function via a variety of mechanisms. The cross-linking (-sheets or cross-structure) abilities of matrix proteins and the induction of the downstream signalings are two of these mechanisms. This may occur as a result of the accumulation of AGEs in the kidney. (11) The development of AGEs on extracellular matrix proteins is linked to diabetic glomerulosclerosis because this process modifies matrix-matrix interactions as well as cell-matrix interactions. For instance, non-enzymatic glycations of type IV collagen and laminin lower their capacity to interact with negatively charged proteoglycans, which results in an increase in the vascular permeability to albumin. (12) Additionally, the development of AGEs on different types of matrix proteins inhibits their breakdown by matrix metalloproteinases, which contributes to the thickening of the basement membrane and the proliferation of the mesangial cells that are characteristic of diabetic nephropathy. (13)

According to the findings of our research, patients with type 2 diabetes who also had DFS had higher

HbA1c levels. These findings support the hypothesis that inadequate glycemic management may play a role in the development of CKD and DFS in diabetes. In individuals who have CKD, other risk factors such pAVD and polyneuropathy, both of which are known to have a role in DFS, are also present at a higher prevalence. (9)

Xiao et al. (14) conducted research on the connection between renal functional condition and the therapeutic impact and prognosis of foot ulcers in patients with type 2 diabetes mellitus and found that their findings were consistent with ours. Observations were made about the amount of time required for the growth of granulation tissue (GT), the amount of time required for healing (HT), the amputation rate, and mortality. Whatever the stage of the foot ulcers' disease, the GT and HT of the ulcer developed more with the progression of diabetic nephropathy. In actual, the GT and HT of foot ulcers were considerably longer in V and IV phases of diabetic nephropathy than those of III phase, while the situations of their foot ulcers were approximately the same. This was the case despite the fact that their foot ulcers were in about the same condition. GT and HT levels demonstrated a significantly positive linear connection with the severity of diabetic nephropathy (P 0.05) in all of the patients who had foot ulcers and whose conditions were comparable to one another. (14)

According to Ndip et al., A new independent risk factor for diabetic foot conditions that falls under the umbrella of chronic kidney disease (CKD) is end-stage renal disease (ESRD). The risk is further increased in these people by poor foot self-care on the part of patients and by dialysis centres not offering on-site foot care because medical attention is diverted to the dialysis procedure itself. This is in addition to the classic triad of infection, neuropathy, and peripheral arterial disease that operate in these people. (15)

Research Group on Diabetes and Chronic Illnesses, Mexican Social Security Institute, Durango studied the relationship of microalbuminuria with diabetic foot ulcers in type II diabetes patients. Outpatients receiving first-level medical care in offices located in Durango, Mexico, were recruited for this clinical trial on a cross-sectional basis and randomly assigned to one of two groups: (a) patients with diabetic foot ulcers or (b) control of group patients who did not have diabetic foot ulcers. Within the scope of the investigation were 670 diabetic patients. The duration of diabetes, smoking cigarettes, age, and microalbuminuria all revealed a strong link with diabetic foot ulcers when odds ratio analysis as well as logistic regression analysis was performed.

A prospective study of 94 consecutive patients observed that initial healing success rates for diabetic foot ulcer patients who were hospitalised did not translate into comparable long-term results. This was the conclusion drawn from the study. According to a paper that was published in Diabetes Care and was in agreement with our findings, the presence of nephropathy was found to be a significant predictor of poorer outcomes, whereas age was found to be an independent predictor of global therapeutic success (GTS). This finding was consistent with our findings. During the period of time between January 1998 and December 2000, there were a total of 94 diabetic patients who were hospitalized for diabetic foot ulcers. Of these patients, 89 (63 men) were successfully followed up for an average of approximately 80 months. The only independent predictor of first amputation was diabetic nephropathy, which was also the only cause of first amputation. It was also believed that diabetic nephropathy was a crucial marker of other aspects in long-term prognosis, such as reduced renal function being an independent predictor of healing failure and overall mortality; in conjunction with albuminuria, it was related with amputations. (16)

There are a few problems with the way our study was conducted. One may make the case that the patients seen at a tertiary university center are of a particularly high quality. However, many of the patients who were evaluated only had access to our outpatient clinic as their sole source of medical treatment since they did not have access to any other physicians. We do not believe that the most severe cases or those chosen at random are the only ones we see. This fact is supported by a vast array of fundamental facts pertaining to our patients, such as their ages, lengths of time living with diabetes, body mass indices, serum creatinine levels, and many others. Standardization of diagnosis, therapy, and documentation on an electronic data sheet is a distinct advantage of this trial, which was conducted at a single center.

What clinical implications do our findings have? There is strong evidence that regular screening can prevent DFS and amputations. (17) Early lesions

necessitate treatment with offloading, antibiotics, and local wound care. (18). It is reasonable to assume that the chance of developing diabetic foot disease increases as one progresses from microalbuminuria to end-stage renal failure and hemodialysis (19). High-risk diabetic patients with CKD should be checked for diabetes microvascular complications (DFS) at each and every office visit.

Conclusion:

There was a significant correlation between the severity of renal function impairment and DFS in patients with type 2 diabetes and end-stage renal failure; consequently, it is advised that patients with renal insufficiency be screened more frequently and routinely for the presence of DFS and be provided with specialized care and education on foot care.

Conflict of Interest:

The authors declare that they have no competing interest.

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