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Frequency of Neuropathic, Vascular and Neuroischemic Foot Ulcers in Diabetes and Risk of Infection with these Etiologies

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Abstract

Background: Diabetic Foot Ulcers (DFU) is a hazardous consequence of diabetic foot disease with a very high rate of amputation. Diabetic foot ulcers may be neuropathic, ischemic or neuro-ischemic in nature and the type of DFU influences the course of the disease and it is important in deciding the management of foot ulcer.

Objective: To determine the frequency of vascular, neuropathic and neuro-ischemic foot ulcers and to study the association of each type with the presence of infection presenting in a tertiary care diabetes center.

Material & Methods: This descriptive cross sectional study was conducted from July 2019 to December 2019 in diabetes management center services hospital Lahore. Adult patients presenting with diabetic foot ulcers were assessed for neurological status and vascular sufficiency in the lower limbs. Presences of foot deformity and wound status were recorded. Neuropathy was checked by 10 g monofilament test and 128 Hz tuning fork test and vasculopathy was checked by measuring blood pressure in brachial and posterior tibial arteries and calculating Ankle Brachial Index (ABI) in both limbs. Clinically ulcer grade was determined by Wegener's grading and probe test. And presence of infection was confirmed by swab test of wound.

Results: 132 patients were included in this study, of whom 92 (69.7%) were males and 40 (30.3%) females, the mean age was 55.0 ± 15.50 years. DFU was neuropathic in 97 (73.5%), ischemic in 08 (6.1%) and neuro-ischemic in 27 (20.4%) cases. 38.6% patients had wound infection. Among the neuropathic ulcers 39% were infected and among ischemic ulcers 50% were infected and among neuro-ischemic ulcers 33% patients were infected.

Conclusion: Peripheral neuropathy is the commonest pathology underlying diabetic foot ulcers presenting at tertiary care centers. Early detection of neuropathy in these patients and efforts focusing on foot care should help prevent ulceration with its often grave consequences.

Keywords: Diabetic foot ulcer; Neuropathy; Ischemia; Neuro-ischemic foot ulcer; Wound infection.

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Introduction

The major complication of diabetes mellitus is diabetic foot ulcer, and it is also the major component of the diabetic foot [1]. Studies show that in Pakistan the prevalence of diabetic foot ulceration is between 4% and 10% and the rate of amputation after foot ulceration is 8%-21% [2]. Diabetic foot lesions have many health and socioeconomic problems holding adverse effects on the quality of life of the patient and imposing a heavy economic burden on the patient's family and society as well [3]. Diabetic foot problems are one of the common reasons for hospitalization of diabetic patients [4]. After the appearance of foot ulcers, the cost of care for patients with DFS is 5.4 times higher in the first year and 2.8 times in the second year as compared to diabetic patients without foot ulcers [4].

The contributory factors that result in foot ulcer development are peripheral neuropathy, peripheral vascular disease, and poor glycemic control, foot deformity, past foot ulcer history, previous amputation, visual impairment, diabetic nephropathy, vascular assessment and cigarette smoking [1]. Certain other factors, such as, barefoot walking, illiteracy, low socioeconomic status, late presentation by patients, ignorance about diabetic foot care and belief in the alternative systems of medicine contribute to this high prevalence [5].

Diabetic Foot Ulcers (DFUs) occur due to loss of sensations, smaller blood vessels angiopathies and uncontrolled blood sugar levels [2]. The hyperglycemic state which results in activation of metabolic pathways which afterwards leads to development of vascular insufficiency, nerve damages leading in turn to ulceration in lower extremity due to plantar pressures and foot deformity [6].

Diabetic neuropathy is a common complication of both types of diabetes, which affects above 90% of the diabetic patients [7]. Experimental evidence and clinical observations suggest that functional disturbance of the peripheral nervous system, especially neuropathy; can lead to impaired connective tissue healing [8]. As a result of longstanding hyperglycemia, a downstream metabolic cascade leads to peripheral nerve injury through an increased flux of the polyol pathway, increased advanced glycation end products formation, excessive release of cytokines, activation of protein kinase C and exaggerated oxidative stress, and also other confounding factors. Very long axons originating in the small neuronal body are vulnerable at the most distal side as a result of malnutrition axonal support or environmental insults. Sparse vascular supply with impaired auto regulation leads to hypoxic damage in the nerve. These dual influences exerted by long term hyperglycemia are crucial for peripheral nerve damage, resulting in distal predominant nerve fiber degeneration [9].

Microvasculature in the skin is comprised of nutritive capillaries and thermoregulatory arteriovenous shunt flow, that is regulated through the complex interaction of neurogenic and neurovascular control. Therefore, very close association between a properly functioning nervous system and a functional micro vascular system becomes clear. The interplay among impaired nerve axon reflex activities, endothelial dysfunction, and micro vascular dysregulation are very important factors in the poor healing of wounds. Initially, micro angiopathic changes are thickening of the capillary basement membrane and hyperplasia of the endothelium. This causes vasoconstriction leading

to reduced oxygen tension and hypoxia and neuronal ischemia. Afterwards, hyperglycemia will further lead to different pathways causing sorbitol accumulation, increase in diacylglycerol levels and oxidative stress leading to nerve damage [8,10].

Micro vascular insufficiency in turn leads to impaired micro vascular blood flow to the skin this results in abnormal contraction of the arterioles and arteries of the skin. Dry skin leads to fissures and ulcer development helps in further seedling of infection and gangrene [10]. Infections occur in up to 58% of patients presenting with a new foot ulcer in diabetes [11]. DFU infections are mono-microbial as well as poly-microbial [12-16].

The elevated systemic glucose levels seen in diabetic patients are the root cause of many micro and macro vascular complications that ultimately can affect angiogenesis. Insufficient angiogenesis plays a significant role in the pathogenesis of diabetic wound healing and micro and micro vascular disease, leading to integrity loss, detachment and increased susceptibility to apoptosis [17].

Diabetes leads to chronic vascular disease in which disordered glucose homeostasis triggers abnormalities resulting in dysfunction of almost every organ, deriving, in part, from vascular disturbance. Several mechanisms influencing the vascular properties in diabetes have been proposed. Two mechanisms that have received wide attention include the polyol pathway and diacylglycerol-mediated activation of protein kinase C. Elevated flux of metabolites through the polyol pathway results increased generation of sorbitol, decreased myoinositol uptake, and diminished Na/K ATPase activity and has been suggested as a means of cellular dysfunctions in the setting of hyperglycemia [18].

Rationale

Foot ulcer has the poorer outcome, by knowing the frequency of neuropathic foot ulcer, vascular foot ulcer, mixed foot ulcer and the risk of infection which can be highly influential and significant in management of foot ulcer and by timely intervention for each of the above conditions can improve healing of foot ulcer, as well as decrease in recovery time and can prevent amputations and patients disability.

Objective

To determine the frequency of neuropathic, vascular and mixed type of ulcers in diabetes and to study the associations of each type with the presence of infection presenting in a tertiary care diabetes center.

Operational Definitions

Diabetic foot

Diabetic foot was defined as the foot of diabetic patients with ulceration, infection and/or destruction of the deep tissues, associated with neurological abnormalities and various degrees of peripheral vascular disease in the lower limb.

Peripheral neuropathy

Peripheral neuropathy means numbness, decreased or loss of sensation, and/or pain in the feet, legs, or hands confirmed with tuning fork test, deep tendon reflexes.

Vasculopathy

It is a general term used to describe any disease affecting blood vessels confirmed with ABI.

Ankle Brachial Index (ABI)

ABI is the ratio of blood pressure at the ankle to the blood pressure in the arm. Systolic blood pressure was measured at the ankle in dorsalis pedis, and at the arm in the brachial artery, by using hand held doppler with a frequency of 8 mHz, while a person is at rest and ratio was taken, ABI>0.9 was taken as normal and the subject which have ABI<0.9 was diagnosed to have PAD. When ABI is between 0.4 and 0.9 the subjects is having mild to moderate PAD, subject is considered having severe PAD when ABI<0.4.

Materials and Methods

Study design: Cross sectional

Setting: Diabetes management center, Services hospital Lahore.

Duration of study: 1st July 2019 to 31st December 2019

Sample size: Sample size of 132 was to improve statistical efficacy.

n=z2pq/d2 (Where z=1.96, p=5% (prevalence of diabetic foot ulceration), q=100-p, d=5% at 95% confidence level, n=73)

Sampling technique: Non Probability, Consecutive Sampling

Inclusion criteria: All adults above 18 years, Adults with diabetic foot ulcers

Exclusion criteria: Who did not gave consent, or with serious co-morbid condition requiring emergency referral.

Data collection

After ethical committee approval of the proposal of the study, patients were recruited from diabetes management centre. After taking informed consent of the patients they were asked specific questions about diabetes history then he or she had undergone specific clinical evaluation. Blood pressure was taken. Vascular and sensory assessment of lower limbs was done. Assessment of foot deformity or wound was done. Neuropathy was checked by 10 g monofilament test and 128 Hz Tuning Fork test. For vasculopathy, patients were checked clinically by palpating popliteal, posterior tibial and dorsalis pedis arteries of both limbs. Then ABI of the patient was done on both sides. Biochemical tests like HbA1c, complete blood count, renal function tests were done. Swab of the wound was taken to identify infection. Modified proforma from the model of care for the diabetic foot was used.

Data analysis

SPSS version 25.0 was used to enter and analyzed the data. Quantitative data like age, Hb, TLC, etc. were presented as means and standard deviation and qualitative data like DFU type, Wegener's stages and neuropathy etc. were presented as frequency and percentages. Stratification of DFU type was done with age groups, gender, duration of DM, control of DM, eGFR categories, retinopathy, macro-vascular complications, wound infection and Wegener's grade. Stratification of wound infection was done with Wegener's grade too.

Results

132 patients included in this study, 92 (69.7%) males and 40 (30.3%) females. Duration of DM was 0-10 years in 72 (54.5%), 11-20 years in 49 (37.1%), 21-30 years in 8 (6.1%) and 3 (2.3%) cases .07 (5.3%) cases had HbA1c<7 and 125 (94.7%) cases had HbA1c ≥ 7.

Mean age was 55.0+15.50 years. Mean HbA1c was 11.46 ± 1.82 g/

dl. Mean TLC was 10300 ± 9610 micro liter. Mean platelet count was 308620 ± 107360 micro liters. Mean serum creatinine was 1.13 ± 0.69 mg/dl. Mean cholesterol was 199.9 ± 67 mg/dl. Mean triglyceride level (TG) was 135 ± 56.1 mg/dl.

Retinopathy was present in 18 (13.6%) cases and 78 (59.1%) cases had eGFR ≤ 60 ml/min. Macro-vascular complications were present in 26 (19.7%).

DFU was neuropathic in 97 (73.5%), ischemic in 08 (6.1%) and neuro-ischemic in 27 (20.4%) cases (Table 1). Stratifications were also done as given in (Tables 2 and 3). Wegener's grade of DFU was 1 in 68 (51.5%), 2 in 32 (24.2%), 3 in 25 (18.9%) and 4 in 07 (5.3%) cases. 51(38.6%) patients had wound infection. Association of DFU type with age groups (p=0.0001) and Wegener's grade (0.025) was statistically significant. Association of wound infection with Wegener's grade was also statistically significant (p=0.000). Overall previous amputation rate was 16.7%, Below Knee Amputation (BKA) was found in 6%, Tarso-Metatarsal (TMA) in 1.6%, digital in 9.1% cases.

Table 1: Type of diabetic foot ulcer in patients (n=132). *: Most common etiology of DFU was neuropathy.

DFU type	Frequency	Percentage
Neuropathic	97	73.7*
Ischemic	8	6.1
Neuro-ischemic	27	20.4
Total	132	100

Table 2: Comparison of DFU with effect modifiers. *: Middle to old age cases had significantly more risk to have mixed neuro-ischemic pathology for DFU. **: Majority cases had not adequately controlled DM.

		DFU Type			
		Neuropathic	Ischemic	Neuro-ischemic	
Age groups	18-28 years	2	1	0	0.0001*
	29-38 years	3	0	4	
	39-48 years	17	4	1	
	49-58 years	38	0	14	
	59-68 years	30	2	5	
	69-78 years	7	0	3	
	79-88 years	0	1	0	
Total		97	8	27	
Gender	Male	64	5	23	0.14
	Female	33	3	4	
Total		97	8	27	
Duration of DM	NewOnset-10 years	50	7	15	0.57
	11-20 years	38	1	10	
	21-30 years	6	0	2	
	31-40 years	3	0	0	
Total		97	8	27	
Control of DM	HbA1c<7%	6	0	1	0.69
	HbA1c ≥ 7%**	91	8	26	
Total		97	8	27	

Table 3: Comparison of DFU with presence of wound infection and Wegener's grade. *: Macrovascular complications and retinopathy were not as frequent findings as compared to their absence in our study cases. Majority of cases had eGFR ≥ 60 ml/min.

		DFU type			
		Neuropathic	Ischemic	Neuro-ischemic	
Retinopathy	Yes	12	1	5	0.71
	No	85	7	22	
Total		97	8	27	
eGFR category	≥ 90	38	3	13	0.93
	60-89	42	4	11	
	30-59	15	1	2	
	15-29	1	0	1	
	< 15	1	0	0	
Total*		97	8	27	
Macro-vascular complication	Yes	19	1	6	0.83
	No	78	7	21	
Total*		97	8	27	

Table 4: Comparison of wound infection with Wegener's grades. *: Majority had non-infected wound.**: Majority had Wegener's grade 1&2 ulcers. ***: Risk of gangrene development was significantly higher in mixed neuro-ischemic type of ulcer. ****: Wound infection was significantly more common in Wegener grade 3&4.

		DFU type			
		Neuropathic	Ischemic	Neuro-ischemic	
Wound Infection*	Yes	38	4	9	0.67
	No	59	4	18	
Total		97	8	27	
Wegener's grade**	Superficial Ulcer Not Infected	51	5	12	0.025***
	Deep Ulcer, with or Without Cellulitis, No Abscess or Bone Involvement	23	3	6	
	Deep Ulcer with Bone Involvement or Abscess Formation	21	0	4	
	Localized Gangrene (toe, forefoot, heel	2	0	5	
Total		97	8	27	
		Wound Infection			
		Yes		No	
Wegener's grade	Superficial Ulcer Not Infected	3		65	0.000****
	Without Cellulitis, No Abscess or Bone Involvement	24		8	
	Deep Ulcer with Bone Involvement or Abscess Formation	22		3	
	Localized Gangrene (toe, fore foot, heel)	2		5	
Total		73		81	

Discussion

Several population-based studies indicate a 0.5%-3% annual collective incidence of diabetic foot ulcers. The prevalence of foot ulcers reported varies from 2% to 10% [19,20]. Diabetic foot complications are the most common problems throughout the globe, resulting in devastating economic crises for the patients, families and society [21]. Peripheral sensory neuropathy, deformity, and trauma are the most common features underlying diabetic foot ulcers although other risk factors such as calluses, edema, and peripheral vascular disease

have also been identified as etiological factors contributing to the development of diabetic foot ulcers.

In this study, a number of risk factors were assessed, associated with foot ulcer, in order of importance were longer duration of diabetes, and HbA1c levels. Ulcer frequency was more in males and importantly, advancing age had been observed as a contributing factor to foot ulceration in diabetic patients in many studies [22]. Frequency of foot ulcers was determined high above the age of 50 in current study, which is comparable to another study by Khan et al. [23].

Neuropathy is a major factor contributing to DFU, so because of insensitive foot and loss of position sense, patients injure their feet without knowing and cannot avoid injury so healing is compromised [23]. Reduced foot pulses independently predict patients at risk of foot ulcer, and so may be a realistic clinical alternative to more sophisticated peripheral vascular assessments but Ankle/brachial pressure index has been identified as an independent risk factor [24].

Younis et al. shown in his study Neuropathic Ulcer 74%, Neuro-ischemic Ulcer 19%, Ischemic Ulcer 7% which are comparable to my study that shows neuropathic 73.7%, Ischemic 6.1% and Neuro-ischemic 20.4% [25]. Other studies show approximately 45%-60% of all diabetic foot ulcerations are purely neuropathic, whereas 45% have both neuropathic and ischemic components [26].

Shahbazian et al. [27] showed that 33.3% of patients with a DFU of grade 1 or higher, as comparison our study; where 13.6% cases had retinopathy. 59.1% cases had eGFR ≤ 60 ml/min, Macro-vascular complications were 19.7%. These co-morbid states might lead to the development of foot ulcers due to generalized ischemia, oozing ulcers in edematous feet, chronic eczema, infection and immobility [23].

In a study done by Jia et al., 37.0% cases had neuropathic, 28.4% had neuro-ischemic, 6.2% had ischemic and 28.4% had other types of foot ulcers. Overall foot ulcer infection rate was 40.1%. Among neuropathic ulcers 42.1% cases, among ischemic ulcers 26.4% cases and among neuro-ischemic ulcers 43.8% cases were infected (p=0.11). Deep ulcer was found in 6.5% cases of neuropathic, 3.8% of ischemic and 7.5% of neuro-ischemic ulcers (p=0.33). 28.4% cases had history of previous amputation. Deep ulcer was found in 11.6% infected cases 5.2% of non-infected cases (p=0.003%) [28]. While in our study 38.6% patients had wound infection. DFU was neuropathic in 73.5%, ischemic in 6.1% and neuro-ischemic in 20.4% cases. 51 (38.6%) patients had wound infection. Among the neuropathic ulcers 39% were infected and among ischemic ulcers 50% were infected and among neuro-ischemic ulcers 33% patients were infected (p=0.67). Among neuropathic ulcers 23.7%, ischemic 0%, neuro-ischemic 33% had Wegener's grade 3/4 (deep ulcer) (p=0.025). Overall previous amputation rate was 16.7% in our study. Deep ulcer was found in 32.9% of infected cases and 9.9% of non-infected cases (p=0.000).

Infection of foot ulcers in diabetic patients is estimated to be the most common cause of diabetes-related admission to hospital and remains one of the major pathways to lower-limb amputation. Presence of peripheral arterial disease or neuropathy reduces the local inflammatory response and classical signs or symptoms of local infection. Even with appropriate care, DFUs can ultimately lead to serious complications such as infection, amputation, and even death. Due to the heterogeneous populations investigated by previous studies, Peripheral Arterial Disease (PAD) is more likely a major risk factor for DFU rather than diabetic foot infection. So once a DFU has become infected then underlying PAD may accelerate the progression of the infection and increase the risk of subsequent hospitalization and amputation. In our study infection rate was more in ischemic DFUs, may be because of number of patients were less and there may be lack of diagnostic facilities in primary health care set up. So we suggest that patients should undergo proper evaluation and it should be done by noninvasive tests like ABI measurements [29].

Conclusion

Majority of our cases were male, middle to old aged, had diabetes duration within 20 years and had HbA1c above desired level. Macro-vascular complications and retinopathy were not frequent findings in our study cases. Majority had non-infected wound and had Wegener's grade 1 and 2 ulcers. Cases with mixed neuro-ischemic etiology were significantly more prone to develop deep ulcers. Wound infection was significantly more common in deep ulcers. Neuropathy was more contributing pathology for DFU in majority of cases as compared to peripheral arterial disease. However middle to old age cases had more risk to have mixed neuro-ischemic pathology for DFU. Early detection of neuropathy in these patients and efforts focusing on foot care should help prevent ulceration with its often grave consequences. DFU healing also takes a long time and can lead to amputation of the lower extremities, thus exacerbating poor quality of life in diabetic population.

Higher rate of infection was found in ischemic etiology as compared to others. But the association was not statistically significant. Higher ulcer grade was found in neuro-ischemic etiology as compared to the others and it was statistically significant.

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