ORIGINAL ARTICLE

Study of Predictive Factors in Diabetic Foot Ulcers: Special Emphasis on Peripheral Arterial Disease

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Abstract:

Background: Studies on diabetic patients with foot ulcers having Peripheral Arterial Disease (PAD) are scarce. In this study, factors that predict diabetic foot ulcer patients' outcome are considered, and differences in predictors between patients with peripheral arterial disease and other patients are noted. *Aim and Objective*: To study the Predicting factors and outcome of Diabetic Foot Ulcers (DFU) in patients with Peripheral Arterial Disease. *Materials and Methods*: Total of 300 diabetic patients with a foot ulcer in two groups; with and without PAD were subjected to a prospective study. Predicting factors and differences in these factors between these two groups were studied. *Results:* After one year of study ulcer did not heal in 23% of the patients. Older age, male sex, larger size of ulcer, peripheral poly neuropathy and PAD were considered as factors predicting healing. After analyses of study with special emphasis on PAD, infection was found to be a new factor in predicting of non-healing of ulcer only in patients with PAD. *Conclusion:* The association of Diabetic ulcers with PAD are significant factors to be taken into consideration while treating such individuals; there is need in the development of multimodal, practically applicable protocols for better management and to bring better results in these patients.

Keywords: Diabetic Foot Ulcers, Peripheral Arterial Disease, Non-healing Ulcers, Polyneuropathy

Introduction:

Development of foot ulcer is one of the debilitating complications in patients with diabetes mellitus. Studies estimate that in diabetic patients the lifetime risk of suffering with a foot ulcer is up to 25% [1]. Management of diabetic foot ulcers requires multimodal approach and long duration treatment. This causes changes in quality of life of patients as well as family [2] and results in significant financial burden [3–5]. Lots of efforts have been put into the development of universal protocols for the management of diabetic foot ulcers in recent years [6], but prospective studies on factors predicting outcome of foot ulcers in diabetes mellitus patients are scarce.

Clinical characteristics in the diabetic patients with foot ulceration have many differences: other than peripheral polyneuropathy which is seen in most of the patients. There are many other factors that may differ among patients, Peripheral Arterial Disease (PAD) are certainly of importance. Peripheral arterial disease is seen in approximately fifty percent of patients having foot ulcers [7] and should be contemplated as a significant factor predicting the outcome [8-9]. Therefore, study on outcome of ulcers in this population of patients with diabetes mellitus is important. In most of the previous studies on diabetic foot ulcers, PAD is considered as one entity and differences in clinical characteristics in individual patients were not considered. The study was carried out with objectives of obtaining detailed information on outcome of diabetic patients having foot ulcer,

including the patients suffering from peripheral arterial disease; analyzing factors that predict healing or delayed/non-healing of the diabetic foot ulcer; and to see if those factors differ in patients having PAD.

Material and Methods:

From 1st September 2013 to 31st August 2018, 300 patients presenting with diabetic foot ulcer, abscess, cellulitis or necrotizing fasciitis to outpatient and inpatient clinics Department of Surgery of BLDE(DU)'s Shri B. M. Patil Medical College Hospital and Research Centre, Vijayapura were included in study. Approval was taken from the Institutional Ethical Committee. Patients included were individuals with new foot ulcer for first time in last one year. Patients were followed-up every month. At the beginning and during monthly follow-up, details were noted on standardized proforma for case taking. Collected data included patients' demographic details, data on co-morbidities and clinical characteristics of ulcers, the details of investigations done and treatment given.

Treatment of Foot Ulcers in Diabetic Patients:

Patients were treated as per standard protocols (International Consensus on the Diabetic Foot) [11], including assessment of blood supply to the foot, medical treatment of PAD, off-loading, pus culture sensitivity of ulcers and antibiotic according to sensitivity for infections, regular bed side and operation room wound debridement as and when required.

Choosing Factors Which Potentially Predict Wound Healing:

Factors affecting the healing of ulcers were chosen on the basis of current literature, suitability for assessing the ulcer in routine practice and opinion of experts. Several specific factors and co-morbidities were investigated along with age, sex and duration of diabetes [10].

Characteristics of Diabetic Foot Ulcers:

Patients were examined following the PEDIS system (International Consensus on the Diabetic Foot) [11-12] and foot ulcers were classified based on five categories i.e., perfusion, extent, depth, infection, touch, pressure and vibration sensations. Perfusion assessment to feet was done by palpating presence of peripheral pulses in foot and by measuring the Ankle–Brachial Pressure Index (ABPI) with the help of handheld Doppler; PAD was diagnosed if two foot pulsations were absent and/or ABPI was <0.9

Size of the ulcer was calculated by multiplying the longest diameter by second longest diameter right angle to the first and ulcers were divided into three sizes : $<1 cm^2$, $1\text{-}5 cm^2$ and $>5 cm^2$.

Ulcer was considered deep if it involved complete thickness of the skin or extending up to the subcutaneous layer and is considered superficial, if it involves only the superficial layers of skin.

Infection was identified based on presence of two or more signs like redness, fever, edema, lymphangitis, pus, local rise of temperature, tenderness, and foul smelling discharge. Specific organism was diagnosed with culture from wound swab.

Peripheral Polyneuropathy (PNP) was said to be present if following tests show abnormal results. Sensation of pressure assessment with 10 g monofilament over plantar aspect of great toe, 1st, 3rd and 5th metatarsal heads, vibration sensation with biothesiometer.

Based on the location ulcers were divided into plantar and non-plantar ulcers.

Three groups were made based on duration of diabetes i.e < 5years, 5-10 years and >10 years.

Based on the duration of ulcer, three groups were made: <1 week, 1week to 3 months and >3months.Three types of wound closure were considered in the study; Secondary Intention Healing (SIH), Secondary Suturing (SS), Split Thickness Skin Grafting (STSG). Total hospital stay of patients was noted and grouped into 0-10 days, 11-20 days, 21-30 days, 31-40 days, 41-50 days and 51-60 days. Number of patients in each group was noted.

Outcome:
Complete healing before the follow-up period up to 12 months was considered as primary efficacy point. Ulcer was said to be healed if all ulcers of foot are healed with epithelial (skin) covering at two consecutive follow ups or ulcer has become fit for secondary suturing or Split Thickness Skin Grafting (STSG) which was taken as secondary efficacy end point.

Statistical Analysis:
Two groups were compared using χ^2 tests for frequency data and Student's t test for continuous data.

Results:
Clinical Outcome:
In 12 months follow-up, healing was noted in 241(77%)of the 300 patients, 36(12%) were still not healed and were on treatment, 15(5%) patients had to undergo above ankle (major) amputations. Fifty one had to undergo minor amputation in group of patients whose ulcers healed.

It was observed that healing of the ulcers were significantly poor (p<0.001) in patients having PAD when compared to patients not having PAD{114(79%) vs. 112(84%), respectively} and mortality rates and rates of major amputations were more in patients with PAD (8% and 9%, respectively) compared to patients not having PAD (2% and 3% respectively; p<0.001). Baseline characteristics in patients having PAD compared with patients not having PAD are given in Table 1.

Factors Predicting Healing:
Table 2 shows the potential predictors of non-healing and its associations: elderly age, male sex, larger ulcer size, PNP and PAD. As we had hypothesized that, there will be differences in factors that affect the delayed or non-healing in patients having PAD and those not having PAD, data was noted separately for these two groups. Except PNP all other factors were found to be independent factors for healing in PAD group. The infection was found as a separate independent factor for non-healing group. Elderly age, ulcer involving larger area, immobilized or bed ridden patients, chronicity of ulcer were independent factors predicting poor healing in group not having PAD. After analysis of the odds of non-healing in patients with PAD and status of infection, it was found that odds of non-healing are significantly increased in group having PAD as compared to group not having PAD.

Table 3 shows relation of PAD with infection. Table 4 shows cases admission. Table 5 shows bacterial growth.Table 6 shows wound closure. Table 7 shows co-morbidities.

Table 1: Demographic Profile of Subject						
Parameters		**Patients with PAD (n =166)**		**Patients without PAD (n=134)**		*P*
		N	**%**	**N**	**%**	
Age (years) Mean ± SD		69.1 ± 11.2		60.5 ± 12.3		<0.001*
Sex	**Male**	109	65.6	85	63.6	0.490
	Female	57	34.4	49	36.4	
Duration of diabetes	**<5 years**	22	12.9	20	14.9	0.265
	5–10 years	24	14.7	23	17.4	
	>10 years	120	72.4	91	67.7	
Deep ulcer		87	52.7	59	35.8	<0.001*
Duration of ulcer						
Size of ulcer	**<1 cm^2**	57	34.4	53	39.5	NS
	1-5 cm^2	85	51.5	71	53	
	>5 cm^2	24	14.2	10	7.5	
Duration of ulcer	**<1 week**	20	11.5	29	21.7	<0.001*
	1 week–3 months	96	58	77	57.5	
	>3 months	50	29.5	28	20.8	
Plantar location		68	40.9	74	55	<0.001*
Polyneuropathy		128	77.2	106	79.3	0.429
Infection		101	60.9	89	53.4	0.016*

*Note: * significant at 5% level of significance (p<0.05), NS - Not significant*

Table 2: Predictor Variables

Predictor variables		Outcome: healing		
		OR	**95% CI**	*P*
Age	**Per 10 year increase**	1.31	1.17–1.48	<0.001*
Sex	**men vs. women**	1.47	1.07–1.96	0.018*
Duration of diabetes	**5–10 vs. <5 years**	0.95	0.56–1.65	0.712
	>10 vs. <5 years	0.99	0.69–1.60	
Depth of ulcer	**Deep vs. superficial**	1.66	1.25–2.20	<0.001*
Size of ulcer	**1–5 vs. <1 cm^2**	2.25	1.60–3.17	<0.001*
	>5 vs. <1 cm^2	4.22	2.64–6.72	
Duration of ulcer	**1 week to 3 months vs. <1 week**	1.81	1.15–2.85	<0.001*
	>3 months vs. <1 week	2.61	1.60–4.27	
Location, plantar vs. non-plantar		0.73	0.55–0.98	0.035*
Polyneuropathy, yes vs. no		1.41	0.98–2.04	0.065
Infection, yes vs. no		1.47	1.09–2.00	0.012*
PAD, yes vs. no		2.31	1.72–3.10	<0.001*

*Note: * significant at 5% level of significance (p<0.05)*
OR - Odds ratio, CI - Confidence Interval

Table 3: Relation of PAD with Infection

OR (Non-healing)			
NO PAD	**Infection**	Negative	1.01
		Positive	0.98
PAD	**Infection**	Negative	1.45
		Positive	2.10

OR - Odds ratio

Table 4: Presentation at Admission of Cases

Mode of presentation	No of patients
Ulcer	110
Abscess	75
Cellulitis	84
Necrotizing fasciitis	31

Table 5: Bacterial Growth	
Organism	**No of patients**
Sterile	110
P.aerogenosa	40
P. valagaris	12
S.aureous	86
Klebsiella	15
E.coli	25
St. pyogenes	6
Citrobactor	6

Table 6: Mode of Wound Closure	
Mode	**No of patients**
Secondary Intention Healing (SIH)	153
Secondary Suturing (SS)	53
Split Thickness Skin Grafting (STSG)	94

Table 7: Co-morbidities	
Co-morbidities	**No of patients**
Chronic Obstructive Pulmonary Disease (Smoker)	22
Hypertension	84

Discussion:

This is a prospective study on factors determining outcome of diabetic foot ulcers. In this study, 77% of healing was observed requiring minor amputions in few patients, major amputation had to be done in 5% of patients. It was observed that healing rates of ulcers in patients having PAD were considerably poor. Differences in the predicting for the healing and non-healing of diabetic foot ulcers in patients with and without PAD were noted. Wound infection which is one of the important factors affecting wound healing was found predictive only in group having PAD. It was found not significantly affecting wound healing in group without PAD as infection could be effectively controlled with specific antibiotics in this group but in group with PAD infection could not be controlled effectively in spite of specific antibiotic administration.

Our outcomes are comparable with study conducted by Jeffcoate *et al*. [17] which showed healing in 66% patients and amputations were done in 5% patients with almost same prevalence of PAD.

In our study, it was found that presence of infection and PAD were associated with poor outcome in healing of the ulcers (Fig.1); which showed association between PAD and infection as an important finding in our study. This type of association was not noted in the group not having PAD. This indicates that in this group of patients specific antibiotic and surgical debridement seem to be sufficient for the ulcers in foot with good perfusion. In another study, association between PAD, infection and poor outcome was noted: PAD was noted as independent factor predicting infection-related mortality in that study with majority of outpatients with type 2 diabetes [18].

Little is known about the pathophysiology of wound infection and effectiveness of antibiotics in patients with inadequate perfusion to foot. As of now in patients with PAD reason for more frequent infection and the reason for more
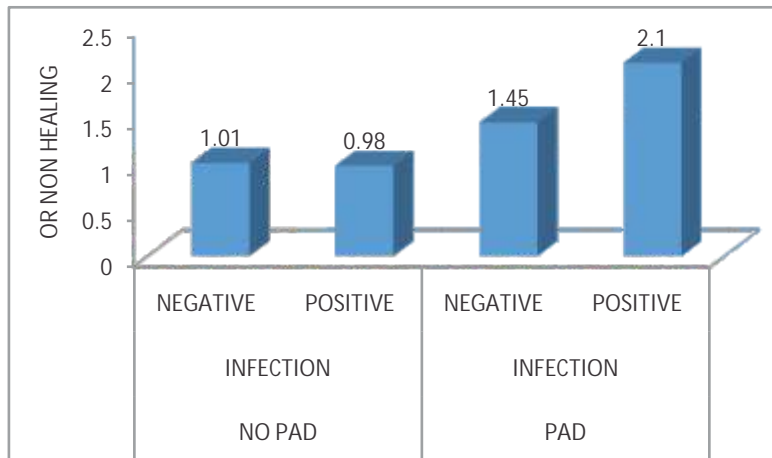
Fig. 1: Presence of Infection and PAD

difficulty in treating it with antibiotics is not clearly understood. In previous studies it has been shown that there can be significantly decreased levels of antibiotics in foot tissues because of decreased blood flow in PAD patients [19].

Interestingly, depth of the ulcer was not related with healing or non-healing in our study. The results of patients not having PAD in this study were relatively favorable: healing was achieved in 84% patients, 2% had to undergo a major amputation. In these patients, peripheral neuropathy causing defect in protective sensation resulted in poor outcome of foot ulcers indicating loss of sensation is not only cause for ulcer formation but it is also one of important factors affecting wound healing. This may be because the conscious protection of the wound site in patients with normal tactile sensation. PNP could be associated with other factors delaying wound healing.

There are several limitations to our study. In this study patients who had an ulcer 1 year prior to presentation were excluded, so it is possible that recurrent ulcers were excluded. Hence, results in our study might have overlooked the chances of delay in healing of recurrent foot ulcer in diabetic patients. Our study is based on results data for

which can be easily assessed like antibiotics used and reperfusion; in this way, our study findings are useful for management of diabetic foot ulcer.

Conclusion:

The findings in our study have many important inferences. Clinical characteristics of ulcer as well as other important clinical characteristics found to influence the results in foot ulcers of diabetic patients. A multimodal approach by surgeons who are experienced with the management of different types of foot ulcers in diabetic individuals is required in order to segregate the difficult cases and use suitable modalities of treatment. It is noted that individuals having PAD show significant difference in clinical findings, factors predicting outcome and the end results of treatment. Therefore, we recommend that those diabetic patients with foot ulcer having PAD and not having PAD must be considered as two different disease entities. The frequent association of infection and decreased perfusion in patients with PAD are significant factors to be taken into consideration while treating such individuals; there is need in the development of multimodal, practically applicable protocols for better management and to bring better results in these patients.

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