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Evaluation of Role of Vasculopathy versus Neuropathy in the Causation of Diabetic Foot

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ABSTRACT

Objectives: To evaluate the role of vasculopathy versus neuropathy in the causation of diabetic foot.

Methods: This was a single-center, retrospective, observational study conducted at a tertiary-care center in India. A total of 50 patients with diabetic foot ulcers admitted to hospital between March 2003 and February 2005 were included in the study. Fasting blood sugar and postprandial blood sugar levels were collected and glycosylated hemoglobin (HbA1C) was evaluated from all the patients.

Results: In this study, majority of patients (40%) belonged to the age group of 50-60 years. There was male predominance in occurrence of diabetic foot. Twenty-six (52%), three (6%), and 21 (42%) patients had neuropathy, vasculopathy and both vasculopathy and neuropathy, respectively. Fifteen patients underwent amputations in diabetic foot. Forty-two (84%) patients had uncontrolled HbA1C and majority of patients have uncontrolled fasting blood glucose level (>130 mg/dl) by the time they presented with diabetic foot complications. Infection was observed in 20 (40%) patients which played a crucial role in development of diabetic foot.

Conclusion: Neuropathy has a predominant role in causing diabetic foot lesions compared to vasculopathy. This study supports the need of using a standardized non-invasive examination of neuropathy and vasculopathy in diabetic clinics.

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Keywords: Diabetic foot; diabetic neuropathy; foot ulcer; peripheral vascular disease; vasculopathy

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INTRODUCTION

Diabetes is the most common factor for the cause of foot ulcers, infection and ischemia, which are among the most serious complications of diabetes leading to hospitalization and lower limb amputations [1, 2]. Compromise in blood supply from the microvascular disease in association with lack of sensation because of neuropathy are the underlying causes of diabetic foot lesions. Diabetic patients are 15 to 30 times more promising to have an eventual amputation in diabetic foot disease compared to the non-diabetic patients [3]. Load of diabetic foot disease and ulceration is set to increase further due to co-existence of causative comorbidities such as peripheral vascular disease (PVD) and peripheral neuropathy [1]. Diabetic peripheral neuropathy (DPN) is well accepted as an important pathophysiological risk factor for developing foot ulcers and affects approximately 50% of diabetic patients [4, 5]. The bulk of foot ulcers appear from minor trauma in the presence of sensory neuropathy [5-7]. Vasculopathy is also presumed to play a role in some individuals, but it remains unreadable whether this is primarily due to peripheral macrovascular disease, impaired cutaneous circulation or both [8].

Prevention through identification of high-risk individuals represents the most efficient way to step-down the rate of ulcer formation and leg amputation in diabetic patients. Diabetic foot currently suggests that risk classification system should be based on the presence of signs of PVD, sensory neuropathy and foot deformities [9]. Various techniques are available to detect and measure the abnormalities. Vibration perception threshold (VPT) is measured by a biothesiometer and cutaneous pressure perception threshold is measured by monofilaments are the most commonly used quantitative sensory tests [9]. However, additional significant information may be obtained from simple, non-invasive testing such as Doppler ultrasound examination from which the ankle/brachial systolic blood pressure index (ABI) can be derived. Accordingly, this study compared the

standardized non-invasive tests of peripheral neuropathy and angiopathy with the methods used in routine clinical practice for identification of individuals at risk of developing diabetic foot problems. To our knowledge, there is no published study that describes the relative causes of neurological and vascular abnormalities to the overall risk of foot ulceration. Thus, this study was conducted to evaluate the role of vasculopathy versus neuropathy in the causation of diabetic foot by using multivariate techniques.

Methods

Study design and patient population

This was a single-center, retrospective observational study conducted at a tertiary-care center in India. A total of 50 patients with diabetic foot ulcers admitted to the hospital between March 2003 and February 2005 were included in the study. Signed inform consent form was taken from all the patients. Subjects with other causes of vasculopathy and neuropathy, embolism, thrombangitis obliterans (TAO), aneurysms, post-thrombotic ulcer, spinal cord compression (spondylosis and spondylothiasis), metabolic neuropathies, nutritional neuropathies and toxic neuropathies were excluded from the study.

Study procedure

All patients were previously diagnosed with diabetic foot ulcers and were on treatment with either diet therapy, oral hypoglycemic agents, insulin or in any combination of the same. All patients were admitted with symptoms suggestive of vasculopathy or neuropathy or symptoms related to other systemic disorders. On admission, diabetic patients were treated medically by insulin (dose adjusted based upon the blood sugar level), diabetic diet, and sugar restriction. Foot care was advised to diabetic patients. Some of the patients responded well to the conservative treatment i.e. control of diabetes and regular wound dressings. Some of the patients required wound debridement (mechanical complications/enzymatic), incision and drainage (abscess and cellulitis) and minor amputations. Only few patients required major amputations. A detailed examination about signs suggestive of peripheral nerve dysfunction such as ankle reflex, timbed vibration sense, position sense, unipedal stance, muscle power, impairment of pain and temperature sensation, and monofilament sensation were recorded. Assessment of the above mentioned signs were explained below:

a) Ankle reflex: Presence or absence of ankle reflexes were noted using a high quality round

neurological hammer with adequate weight. The absence of bilateral ankle reflexes especially in the presence of other reflexes was considered as highly suggestive sign of peripheral neuropathy.

b) Timbed vibration sense: Vibration sense was assessed using a 128 Hz tuning fork. Vibration sense was assessed first at the metatarsophalangeal joint, secondly at the medial malleolus and finally at the tibial tuberosity. Before testing the impaired areas, an unimpaired area such as sternum or clavicle was tested to know the patient vibration feel experiences. In patients who were unable to feel the vibration at the above mentioned points for a minimum period of 10 seconds neuropathy was suggested. In patients who could feel the vibration of 10 seconds or more, it was suggested that peripheral neuropathy was not present.

C) Position sense: Position sense was tested bilaterally at the great toe. The medial or lateral aspects of the great toe were held and moved in small distances at 0.5–1 cm up or down at random intervals without giving any verbal hints to the patients. A correct response was identified if the patients could feel the motion and identify the direction of the movement exactly. Patients who identified the movement in atleast eight out of 10 chances were considered as the normal response and fewer responses than eight out of 10 responses were considered as the highly suggestive signs of peripheral neuropathy.

d) Unipedal stance: Each patient was given three chances to stand as long as possible on one foot, initially on the right leg then after the left leg and then on the foot of his/her choice. Patients who identified to stand on one foot for more than 10 seconds in any of the three chances were considered as the normal response. Patients who were unable to stand on one foot for a minimum of 10 seconds in all the three chances were considered as peripheral neuropathy.

e) Muscle power: Power of the muscles with special reference to the muscles of the leg, ankle and foot were examined (i.e. tibialis anterior, tibialis posterior, peronei gastrocnemius, ext digitorum longus, flexor digitorum longus, ext hallicus longus and ext digitorum brevis). The responses were graded accordingly from grade 0 to V. In the absence of other causes of weakness the bilateral impairment of power was considered as suggestive of motor neuropathy.

f) Pain and temperature: Sensation of pain and temperature modalities were examined in the extremities. Pain sensation was tested using a sharp pointed pin. Temperature

sensation was tested using test tubes with hot and cold water at 43°C and 7°C, respectively. In the absence of other causes of such impairment, the bilateral impairment of pain and temperature sensations were taken as suggestive of peripheral neuropathy (especially a fibre type).

g) Semmes Weinstein monofilament: The 10gm of monofilament is used in this study. If the patient is asked to test its presence, this filament is applied to a minimum of five sites on the foot until it buckles, usually occurs at 10g of linear pressure. Patients who were detected with no response in atleast three out of five times were considered as loss of protective sensation.

Data collection

History of specific symptoms of PVD such as intermittent claudication, rest pain, chronic critical leg ischemia, gangrene changes or previous amputation was recorded. To study about the circulation in the lower limb vessels, subjects were advised to duplex ultrasound color imaging of lower limbs. Fasting blood sugar and postprandial blood sugar levels were acquired from all the patients. Glycosylated hemoglobin (HbA1C) was evaluated from all the patients. Renal parameters like blood urea and serum creatinine levels were obtained from all the patients. To identify the presence of diabetic retinopathy, the fundus picture was studied in all patients using an indirect ophthalmoscope. The most common mode of presentation was ulcer and gangrene of the toes or foot abscess and cellulitis.

Results

This was a single-center, retrospective observational study which included a total of 50 diabetic patients with diabetic foot lesions. In this study, majority of patients (40%) belonged to the age group of 50-60 years. The youngest patient was of 38 years, while the oldest patient was 80 years old. There was marked male preponderance (72%) in the occurrence of diabetic foot lesions. In this study, 26 (52%) patients had neuropathy, three (6%) patients had vasculopathy and 21 (42%) patients had combined vasculopathy and neuropathy. The most common symptom of PVD was found to be ulcer in 22 (44%) patients followed by gangrene, rest pain and claudication in 17 (34%), 9 (18%) and 2 (4%) patients, respectively. Among various signs of neuropathy elicited according to the study protocol, monofilament sensation loss (pressure sensation) was one of the most common sign observed in 39 (78%) patients. Baseline demographics of the study population are shown in **Table 1**.

Out of 50 patients with diabetic foot lesions, 47 (94%) patients were diagnosed with neuropathy. Among these 47 patients, the different types of neuropathy were alienated as 30 (60%) sensory motor neuropathy, three (6%) sensory motor neuropathy associated with autonomic neuropathy and 14 (28%) merely sensory neuropathy. Among 50 patients, 21 patients had PVD. In right lower limb, the highest percentage of blood flow was reduced (42.86%) and absent (33.33%) in posterior tibial and dorsal pedis. Similarly, in left lower limb also the highest percentage of blood flow was reduced (57.14%) and absent (19.04%) in posterior tibial and dorsal pedis. Popliteal was least involved vessel in both right and left limbs. In left lower limb, popliteal blood flow was reduced in one (4.76%) patient and absent in two (9.52%) patients. This indicates that in diabetic foot lesions, more distal vessels such as posterior tibial and dorsal pedis have been involved compared to proximal vessels.

Out of total 50 patients, majority of patients (70%) were managed conservatively with regular dressing of wound, wound debridement followed by skin grafting, antibiotics and diabetic control. Fifteen patients underwent amputations in diabetic foot. These 15 (30%) patients who had undergone some form of amputation were diagnosed with vasculopathy. Amputations in diabetic foot of the study population were shown in **Table 2**. HbA_1C is an excellent index marker of long-term diabetes control over preceding 2-3 months. In the present study, almost 42 patients had uncontrolled HbA_1C levels and majority of patients (96%) have uncontrolled fasting blood glucose level (>130 mg/dl) by the time they presented with the diabetic foot complications. Correlation between HbA1C and fasting blood sugar levels in diabetic foot patients were displayed in **Table 3**.

Among the 50 patients, 20 (40%) patients had infection. The most common micro-organisms isolated in order of frequency were *Staphylococcus aureus* in eight (16 %) patients, *Pseudomonas* in five (10%) patients, *Streptococcus* in three (6%) patients, *Escherichia coli* in three (6%) patients and *Klebsiella pneumoniae* in one (2%) patient. Role of infection in diabetic foot patients were shown in **Table 4.** The relationship between diabetes and retinopathy was also studied based on the change in fundus surface. Among the study population, 28 (56%) patients were diagnosed with diabetic retinopathy which was an amalgamation of 23 (46%) cases of background non-proliferative, two (4%) cases of pre-proliferative and three (6%) cases of proliferative diabetic retinopathy. Relationship

between diabetic foot and retinopathy among the study population are demonstrated in **Table 5**.

Table 1: Baseline demographics of all the patients

Variables		**Patients (n=50)**
Age		
30-40, n (%)		5 (10%)
40-50, n (%)		12 (24%)
50-60, n (%)		20 (40%)
60-70, n (%)		7 (14%)
>70, n (%)		6 (12%)
Male, n (%)		36 (72%)
Etiological Factors in diabetic foot		
Neuropathy	Sensory, n (%)	14 (28%)
	Sensory + Motor, n (%)	12 (24%)
Vasculopathy, n (%)		3 (6%)
Vasculopathy + Neuropathy, n (%)		21 (42%)
Symptoms of peripheral vascular disease		
Ulcer/tissue loss, n (%)		22 (44%)
Gangrene, n (%)		17 (34%)
Rest pain, n (%)		9 (18%)
Claudication, n (%)		2 (4%)
Signs of neuropathy		
Monofilament (pressure sensation), n (%)		39 (78%)
Vibration, n (%)		37 (74%)
Reflexes, n (%)		29 (58%)
Pain and temperature, n (%)		25 (50%)
Position sense, n (%)		24 (48%)
Unipedal stance, n (%)		15 (30%)

Table 2: Amputations in diabetic foot of the study population

Treatment	**Patients (n=50)**
Conservatively (dressing debridement, skin grafting, diabetic control, antibiotics), n (%)	35 (70%)
Below ankle joint amputation, n (%)	13 (26%)
Below knee amputation, n (%)	01 (02%)
Hip joint disarticulation, n (%)	01 (02%)

Table 3: Correlation between HbA1C and fasting blood sugar levels in diabetic foot patients

Variables	**Patients (n=50)**
Glycosylated haemoglobin-HbA_1C	
Below 5.6% -- Normal, n (%)	--
5.6-7.0% -- Good control, n (%)	8 (16%)
7.0- 8.0% -- Fair control, n (%)	16 (32%)
8.0-10.0% -- Unsatisfactory, n (%)	24 (48%)
>10.0% -- Poor control, n (%)	02 (04%)
Fasting blood sugar	
<100 mg/dl, n (%)	02 (04%)
101-200 mg/dl, n (%)	19 (38%)
201-300 mg/dl, n (%)	21 (42%)
>300 mg/dl, n (%)	08 (16%)

Table 4: Role of infection in diabetic foot of the study population

Microorganisms	**Patients (n=50)**
Streptococcus	3 (6%)
Staphylococcus aureus	8 (16%)
Pseudomonas	5 (10%)
Klebsiella pneumoniae	1 (2%)
Escherichia coli	3 (6%)
No growth	30 (60%)

Table 5: Relationship between diabetic foot and retinopathy among the study population

Variables		**Patients (n=50)**
Fundus changes		
Non-proliferative background diabetic retinopathy	Without maculopathy, n (%)	19 (38%)
	With maculopathy, n (%)	04 (08%)
Pre-proliferative diabetic retinopathy, n (%)		02 (04%)
Proliferative retinopathy, n (%)		03 (06%)
Normal, n (%)		22 (44%)

DISCUSSION

This study demonstrates that both neuropathy and vasculopathy are the important causative factors of diabetic foot lesions. Diabetic foot infections are a common and potentially serious problem in diabetic patients. In this study, diabetic foot lesions were observed more in the age group of 45–64 years (62%) which is similar to a study by Mayfield JA, et

al. showing that 65% of the study population belongs to the same age group [10]. Though the percentage of age groups differed to some extent, this study indicates that diabetic foot complications usually occur in elderly patients. In our study, more males (72%) were presented with diabetic foot lesions which is comparable with the findings of other studies [11, 12]. This male predominance might be due to associated habits of smoking, alcoholism and type of work etc.

In the current study, majority of the population were diagnosed with neuropathy (94%). In which sensory motor neuropathy was observed in more than half of the study population and can be comparable to a study by Sadriwala QS, et al. showing that 50% of the study population were suffering from sensory motor neuropathy [2]. Thus, neuropathy has a dominant role in causing diabetic foot lesions compared to vasculopathy. Infection was observed in 42% of the study population which is also a contributing factor to diabetic foot lesions.

About 2.5% of diabetic men and women will develop a foot ulcer each year [13]. Most of our patients were presented with foot ulcer (43%) which is similar to the earlier studies [14, 15]. The second most common symptom of diabetic foot lesion was gangrene (33%) which is comparable to a study by Nather A, et al. [16]. When comparing the various non-invasive methods, the highest validity for identifying patients at risk for the diabetic foot was demonstrated for the monofilament (78%) examination. This confirms the findings of other studies, where 10g monofilament test can be used as a simple bed-side non-invasive procedure and was documented as an independent predictor of the development of diabetic foot lesions [9, 17]. This may lead to better prevention of sensory neuropathy and subsequent foot ulceration. However, clinical evaluation of neuropathy by monofilament testing is dependent on the skill and the

interpretation of the individual investigator. There is no universally accepted guideline for monofilament use for the interpretation of the results [18]. Hence, various criteria have been used in this study which is similar to the previously published studies [9, 17].

Debridement has to be careful and often repeated debridement is necessary [19]. Despite well-defined risk factors for diabetic foot ulcer development was available but, finite data are available as to which factors predict amputation in a diabetic foot ulcer episode. In this study, the overall rate of amputation in diabetic patients was 30%. Similar high rate of amputation was also reported in study by Uysal, et al. (32%) and Wang, et al. (29.6%) [20, 21]. This is likely because most of the patients in this study presented to the amputation were having vasculopathy. So, there is a high morbidity particularly in patients with diabetic foot lesions associated with vasculopathy. All the patients who have undergone a major amputation have a high risk of subsequent contralateral amputation and therefore, a surveillance programme for the remaining foot is crucial.

Almost 84% of patients had uncontrolled HbA1c levels by the time they presented with diabetic foot complications. This indicates that uncontrolled glycemic control had increased the risk of amputation. HbA1c is directly related to the average glucose concentration over the lifespan of hemoglobin. Hence, levels of blood glucose assessed by HbA1C would be a better predictor of amputation. The UK study reported that the hazard ratio of death from amputation declines 43% when HbA1c declines by 1% [22]. Majority of patients had uncontrolled blood sugar levels during the complication of diabetic foot which is similar to the results obtained from a study by Pemayun, et al. [23].

In the present study, diabetic retinopathy was observed in 28 (56%) patients. Among them 11, 2, 15 patients had neuropathy, vasculopathy, combined neuropathy and

vasculopathy, respectively. The Beck-Nielsen H, et al. study showed a similar correlation between retinopathy and neuropathy which is comparable to our study results [24]. No correlation could be concluded between vasculopathy and retinopathy as there were only three patients who had vasculopathy in which two patients had background diabetic retinopathy. Even though the neuropathy has the initiating factor for the diabetic foot disease in association with the secondary infection, the vascular component should be considered as the major factor for wound healing and also the deciding factor for limb amputation. Thus, our findings stress the importance of using standardized simple non-invasive testing methods to increase the accuracy of identifying the patients at risk for diabetic foot at the community level.

CONCLUSION

This study shows that neuropathy has a predominant role in causing diabetic foot lesions compared to vasculopathy. Patients should be reviewed frequently for neuropathy and neuroischemic lesions and treated if necessary. This study truly supports the need of using a standardized non-invasive examination of neuropathy and vasculopathy in diabetic clinics. This can be achieved by identifying the high-risk individuals like those with peripheral neuropathy, PVD, foot deformities and previous history of ulcers.

Conflict of Interest Statement-

There is no conflict of interest.

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