Original Research Article

Predictive risk factors for lower limb amputations in patients with diabetic foot ulcer in correlation with Wagner’s grading

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ABSTRACT

Background: Lower extremity amputation in diabetic patients results in high morbidity causing poor quality of life despite high medical expenses. A correlate of risk factors with Wagner's grading of foot ulcers and their improvement with multidisciplinary team approach would form a basis for preventive diabetic foot care guidelines in health care policy. Objectives of current study were to assess the risk factors and role of multidisciplinary team approach in patients undergoing lower extremity amputations with diabetic foot ulcer with different Wagner's grading.

Methods: Prospective data of diabetic patients above eighteen years with foot ulcers admitted in departments of general surgery/general medicine at Vydehi Institute of medical sciences and research centre, between October 2017 to October 2019 were included. Multi-disciplinary treatment approach was adopted and treated accordingly. Patients were followed up for three months to reassess the risk factors for lower extremity amputation and correlated with Wagner's grading system and analyzed using descriptive statistical analysis, SPSS-21.

Results: fifty patients with Wagner’s grade 1-4 of which forty four (88%) males and six (12%) females. Four (8%) of the patients underwent major limb amputation. 18% underwent minor amputation and 16% SSG. 54% were grade 3, 4 on day 1 and 24% patients were grade 3, 4 and 5 after 3 months of follow up (p=0.034).

Conclusions: Clinical assessment of diabetic foot ulcer and identification of risk factors for the nonhealing predicts the favourable outcome in the management of diabetic foot combined with multi-disciplinary team approach strategy.

Keywords: Diabetic foot ulcer, Lower extremity amputation, Wagner’s grading

INTRODUCTION

Diabetes mellitus is one of the leading causes for lower limb amputation1. It is of immense value to identify the predictive risk factors and address them accordingly thereby prevent or decrease disability and medical care cost that could occur from lower extremity amputations. Risk of developing foot ulcer is as high as 25%. It is estimated that diabetes accounts for more than 50% of amputation, 85% of lower amputation in diabetes patients are preceded by foot ulcers.1,2 International Consensus on the diabetic foot and practical guidelines on the management and the prevention of the diabetic foot contains guidelines for quality care and prevention of the diabetic foot ulcer and multidisciplinary team approach for effective treatment consisting of physicians, diabetologists, general surgeons/orthopaedicians and nutritionexperts.3 Current study objective was to assess the risk factors and role of multidisciplinary team approach in patients undergoing lower extremity amputations with diabetic foot ulcer with different Wagner's grading.
METHODS

This was a prospective study was conducted at departments of general surgery and general medicine at Vydehi institute of medical sciences and research centre, Bangalore from October 2017 to October 2019. The data of diabetic patients above 18 years with foot ulcers admitted and treated from October 2017 to October 2019 were included. Multi-disciplinary treatment approach was adopted and treated accordingly. Sample size was 50 patients.

Inclusion criteria

Patient with diabetic foot ulcer Wagner’s grade-1 to grade-4, Age from >18 years. Patients who gave consent to take part in the study.

Exclusion criteria

Traumatic foot ulcer in diabetic patients, Wagner’s ulcer grade 5, patients on hemodialysis, patients not consenting for the study.

Procedure

Patients were categorized according to Wagner’s diabetic foot ulcer grading: grade 0: skin lesions absent, hyperkeratosis below or above bony prominences, grade 1: skin and immediate subcutaneous tissue are ulcerated, grade 2: lesions are deeper and may penetrate to tendon, bone or joint capsule, grade 3: deep tissues are always involved, osteomyelitis may be present, grade 4: gangrene of some portion of the toes or forefoot grade 5: the entire foot is gangrenous. All the patients were subjected to routine and specific investigations as mentioned below and risk factors evaluated. Patients were clinically assessed by multi specialty team comprising Endocrinologist, physicians and surgeons. A standard treatment protocol was followed with regular dressings of foot ulcer, antibiotic therapy, wound excision/debridement, minor/major lower extremity amputations documented as per proforma. Minor amputation was defined as toe disarticulation and major as below knee and above knee amputation. All the patients were followed up at weekly/fortnightly basis initially for a month and at an interval of three months later. The status of the ulcer in terms of healing/progression/non-healing were documented on follow up. Amputated patients were assessed for stump healing/revision if required and status of the counter limb with respect to Wagner’s grade. Investigations done blood CBC, blood sugars (fasting and postprandial) C-reactive protein, serum albumin, lipid profile, HBA1c, ankle-brachial index, renal function tests, arterial Doppler study, ESR, ECG, echocardiography, X-ray foot-AP/Lat/oblique, chest X-ray, culture sensitivity of the discharge from the ulcer. Statistical analysis was done using SPSS-21. Analysis of variance (ANOVA) has been used to find the significance of study parameters between three or more groups of patients, Student t test (two tailed, dependent) has been used to find the significance of study parameters on continuous scale within each group Chi-square/Fisher exact test has been used to find the significance of study parameters on categorical scale between two or more groups, non-parametric setting for qualitative data analysis. Fisher exact test used when cell samples are very small.

RESULTS

Most patients both male 22 (50%) and females 3(50%) are in age group of 51-60 (25) 50% followed by 40-50 (12) 24% (Table 1).

Table 1: Age/gender distribution of patients.

| Age (years) | N | % | Male % | Female % |
|-------------|----|---|--------|----------|
| <40         | 3  | 6.0| 1 2.27 | 2 33.3   |
| 40-50       | 12 | 24.0| 12 27.27| 0 0      |
| 51-60       | 25 | 50.0| 22 50  | 3 50     |
| 61-70       | 6  | 12.0| 6 13.64| 0 0      |
| >70         | 4  | 8.0 | 3 6.82 | 1 16.7   |
| Total       | 50 | 100.0| 44 100| 6 100    |

In our study gender distribution of patients studied were 44 males (88%) and 6 females (12%). Age of the patients presenting with diabetic foot ulcer was found to be 55.48±10.74 (Mean±SD) in this study (Table 1). McColl et al in 1986 reported that 75% of all amputees presented after 60 years of age. In our study 36%, 38% and 16% were Wagner’s grade 2, 3 and 4 respectively on day 1 and 8% are grade 5 after 3 months who invariably ended up with major amputation in due course (Table 2, 9-10).

Table 2: Wagner’s grading distribution of patients at day 1 and after 3 months treatment.

| Wagner’s grading | Day 1, N (%) | After 3 months (%) | % difference |
|------------------|--------------|--------------------|--------------|
| 1                | 5 (10)       | 18 (36)            | 26.0         |
| 2                | 18 (36)      | 19 (38)            | 2.0          |
| 3                | 19 (38)      | 5 (10)             | -28.0        |
| 4                | 8 (16)       | 4 (8)              | -8.0         |
| 5                | 0 (0)        | 4 (8)              | 8.0          |
| Total            | 50 (100)     | 50 (100)           | -            |

Five (10%) of the patients were grade 1 on day 1 and grade1 cases after 3 months was 18 (36%) with a significant improvement of 26%. 18% underwent minor amputation and 16% of the patients have undergone split skin grafting. 4 (8%) are grade 5 after 3 months who underwent major amputation and of them 3 (6%) were grade 3 on day 1 and 1 (2%) patient is grade 2. 54% were grade 3 and grade 4 combined on day 1 and 24% of the patients are grade 3, 4 and grade 5 combined with a significant decrease of 30% of the diabetic foot ulcer burden in the study group (Table 2, 9-10).
Table 3: Urine PCR distribution of patients at day 1 and after three months of treatment.

| Duration       | Urinary PCR (%) | Albumin (%) |
|----------------|-----------------|-------------|
|                | <0.2            | 0.2-1       | >1          | Total       | <3.5      | 3.5-5.5    | >5.5      | Total       |
| Day 1          | 18 (36)         | 25 (50)     | 7 (14)      | 50 (100)    | 42 (84)   | 8 (16)     | 0         | 50 (100)    |
| After 3 months | 23 (46)         | 19 (38)     | 8 (16)      | 50 (100)    | 39 (78)   | 11 (22)    | 0         | 50 (100)    |
| % Difference   | 10.0            | -12.0       | 2.0         | -6.0        | 6.0       | 0.0        |           |             |

P=0.003, significant, paired proportion test, 10% improvement.

Table 4: Arterial Doppler studies of patients at day 1 and after 3 months of treatment.

| Doppler changes | Day 1 (%) | After 3 months (%) | % difference |
|-----------------|-----------|--------------------|--------------|
| 1               | 0 (0)     | 7 (14)             | 14.0         |
| 2               | 30 (60)   | 26 (52)            | -8.0         |
| 3               | 20 (40)   | 17 (34)            | -6.0         |
| Total           | 50 (100)  | 50 (100)           | -            |

P=0.280, not significant, paired proportion test, 10% improvement.

Table 5: Creatinine (mg/dl) distribution of patients studied at day 1 and 3 months after treatment.

| Creatinine (mg/dl) | Day 1 (%) | After 3 months (%) | % difference |
|--------------------|-----------|--------------------|--------------|
| <0.9               | 3 (6)     | 6 (12)             | 6.0          |
| 0.9-1.3            | 24 (48)   | 26 (52)            | 4.0          |
| >1.3               | 23 (46)   | 18 (36)            | -10.0        |
| Total              | 50 (100)  | 50 (100)           | -            |

P=0.280, not significant, paired proportion test, 10% improvement.

Table 6: HbA1c% distribution of patients studied at day 1 and after 3 months.

| HbA1c%   | Day 1 (%) | After 3 months (%) | % difference |
|----------|-----------|--------------------|--------------|
| <6.5     | 0 (0)     | 1 (2)              | 2.0          |
| 6.5-9    | 34 (68)   | 38 (76)            | 8.0          |
| >9       | 16 (32)   | 11 (22)            | -10.0        |
| Total    | 50 (100)  | 50 (100)           | -            |

P=0.280, not significant, paired proportion test, 10% improvement.

Table 7: Ankle brachial index in patients studied.

| Ankle brachial index | Day 1 (%) | After 3 months (%) | % difference |
|----------------------|-----------|--------------------|--------------|
| <0.9                 | 26 (52)   | 23 (46)            | -6.0         |
| 0.9-1.3              | 24 (48)   | 27 (54)            | 6.0          |
| >1.3                 | 0 (0)     | 0 (0)              | 0.0          |
| Total                | 50 (100)  | 50 (100)           | -            |

Table 8: C Reactive protein distribution of patients studied.

| C reactive protein | Day 1 (%) | After 3 months (%) | % difference |
|--------------------|-----------|--------------------|--------------|
| <40                | 22 (44)   | 24 (48)            | 4.0          |
| >40                | 28 (56)   | 26 (52)            | -4.0         |
| Total              | 50 (100)  | 50 (100)           | -            |

P=0.384 not significant, paired proportion test, 6% improvement.

Later, p=0.370, not significant, paired proportion test, 6.0% improvement (Table 3). In our study, ABI had values less than 0.9 in 52% and 46% at day 1 and month 3 respectively, whereas ABI value of 0.9-1.3 was 48% and 54% at day 1 and month 3 respectively. No patients were noted to have ABI values greater than 1.3 (Table 7, 9-10). In our study 4 patients who underwent major amputation, 3 patients ABI was 0.6 and 1 patient ABI was 0.7. In our study, albumin levels of less than 3.5 at day were seen in 42 (84%), between 3.5-5.5 in 8 (16%) and none had levels more than 5.5 (Table 3, 7, 9-10). At the 3month follow up, 39 (78%) patients had low albumin levels of less than 3.5; 11 (22%) patients had levels between 3.5-5.5 and none had levels above 5.5. 8% (4) of the patients underwent major amputation and the average albumin in these patients was found to be at day 1 was 2.825 and at 3 months follow up was 2.325. Low albumin levels (p=0.001) with worsened ABI (p=0.002) and arterial Doppler findings (p=0.003) are seen in patients with Wagner's grade 3, 4 and 5 (Table 4, 7, 9-10).

Albumin levels for different Wagner's grading at day 1 was found to be 3.58±0.45, 2.93±0.47, 3.02±0.48 and 2.05±0.48 for grade 1-4 respectively and at 3 months follow up 3.47±0.36, 3.23±0.38, 2.30±0.34 and 2.88±0.31. Mean albumin levels correlated well with the different Wagner's grading. Low albumin levels can be considered as a marker for lower extremity amputation.

The number of patients who had serum creatinine levels between 0.9-1.3 was 24 (46%) and 26 (52%) at day 1 and month 3 respectively. Patients who had levels above 1.3 decreased from 23 (46%) at day 1 to 18 (36%) at 3 months follow up. Mean creatinine was found to be 2.66±1.25, 3.58±0.94, 3.15±0.88 for grade 3, 4 and 5 Wagner's foot ulcers at 3 months follow up.
High serum creatinine levels correlated with worsening of Wagner’s staging and in patients who underwent subsequent amputation. In our study, levels below 40 of C reactive protein were seen in 22 (44%) and 24 (48%) at day 1 and month 3 respectively. Higher levels of more than 40 were seen in 28 (56%) and 26 (52%) at day 1 and month 3 respectively (Table 2, 8-10).

The CRP values of patients in Wagner’s Grade 3 and 4 at day 1 were 51.45±16.73 and 71.04±13.74 respectively. The mean values were 56.64±20.14, 73.70±13.97 and 42.33±10.40 at 3 months for patients having Wagner’s grade 3, 4 and 5 respectively. The association between high CRP values and subsequent risk of amputation was significant with a p value less than 0.001 (Table 8). In our study, low levels of HbA1c of <6.5 were not seen in any of the patients at presentation, while one (2%) of patients were able to achieve glycemic control at 3 months follow up. 34 (68%) of patients had HbA1c levels between 6.5-9 at presentation and the number increased to 38 (76%) at follow up of 3 months. Very high glycemic index of more than 9 was seen in 16 (32%) of patients on day 1 and the number decreased to 11 (22%) at 3 months. The mean values of HbA1c at day 1 was found to be 8.44±1.03, 8.22±0.47, 8.88±0.92, 9.54±0.96 for the four grades of Wagner’s respectively. At 3 months the mean values were found to be 7.67±0.50, 8.15±0.90, 10.02±1.11, 10.63±1.09 for the four grades and 9.28±0.62 for grade 5 of Wagner’s. Worsening of glycemic control inevitably increased the chances of amputations in the patients (Table 6, 9-10). In our study, monophasic flow on Doppler studies were seen in none at presentation while 7 (14%) showed at 3 months. 30 (60%) and 26 (52%) of patients had biphasic flow at day 1 and month 3 respectively. The number of patients showing triphasic flow at day 1 and month 3 was 20 (40%) and 17 (34%) at day 1 and month 3 respectively. All the 4 (8%) patients who underwent major amputation had monophasic flow on Doppler studies at the time of surgery (Table 4).

**DISCUSSION**

Foot ulcers are a common complication of long standing diabetes mellitus. Up to 25% of patients with DM develop diabetic foot ulcers over their lifetime. Diabetic foot disease, mainly due to neuropathy, peripheral arterial disease, and or infection, often leads to ulceration and possible subsequent limb amputation. High serum creatinine levels correlated with worsening of Wagner’s staging and in patients who underwent subsequent amputation. In our study, levels below 40 of C reactive protein were seen in 22 (44%) and 24 (48%) at day 1 and month 3 respectively. Higher levels of more than 40 were seen in 28 (56%) and 26 (52%) at day 1 and month 3 respectively (Table 2, 8-10).

The CRP values of patients in Wagner’s Grade 3 and 4 at day 1 were 51.45±16.73 and 71.04±13.74 respectively. The mean values were 56.64±20.14, 73.70±13.97 and 42.33±10.40 at 3 months for patients having Wagner’s grade 3, 4 and 5 respectively. The association between high CRP values and subsequent risk of amputation was significant with a p value less than 0.001 (Table 8). In our study, low levels of HbA1c of <6.5 were not seen in any of the patients at presentation, while one (2%) of patients were able to achieve glycemic control at 3 months follow up. 34 (68%) of patients had HbA1c levels between 6.5-9 at presentation and the number increased to 38 (76%) at follow up of 3 months. Very high glycemic index of more than 9 was seen in 16 (32%) of patients on day 1 and the number decreased to 11 (22%) at 3 months. The mean values of HbA1c at day 1 was found to be 8.44±1.03, 8.22±0.47, 8.88±0.92, 9.54±0.96 for the four grades of Wagner’s respectively. At 3 months the mean values were found to be 7.67±0.50, 8.15±0.90, 10.02±1.11, 10.63±1.09 for the four grades and 9.28±0.62 for grade 5 of Wagner’s. Worsening of glycemic control inevitably increased the chances of amputations in the patients (Table 6, 9-10). In our study, monophasic flow on Doppler studies were seen in none at presentation while 7 (14%) showed at 3 months. 30 (60%) and 26 (52%) of patients had biphasic flow at day 1 and month 3 respectively. The number of patients showing triphasic flow at day 1 and month 3 was 20 (40%) and 17 (34%) at day 1 and month 3 respectively. All the 4 (8%) patients who underwent major amputation had monophasic flow on Doppler studies at the time of surgery (Table 4).
than ten years (Table 1). Male patients under went repeated surgeries and re-amputations due to delayed wound healing and vulnerability to ulcer infections. According to the consensus guidelines of foot care, better treatment outcomes are expected if all patients with problems related to the diabetic foot are treated by multidisciplinary treatment teams. Treatment of diabetic foot ulcers requires correcting the local and systemic factors predisposing to ulcer formation. Chances of healing of diabetic ulcer are poor. Most important factor is the adequate blood sugar control. Most diabetic ulcers are infected and removal of the infectious source is very important to the success of healing (Table 6-7, 9-10). Gender distribution of patients studied were 44 males (88%) and 6 females (12%) (Table 1) Diabetic foot was more prevalent in males 4.5%, 95% CI: 3.7-5.2%) than in females (3.5%, 95% CI: 2.8- 4.2%). In our study, age of the patients presenting with diabetic foot ulcer was found to be 55.48±10.74 (Mean±SD) (Table 1). In the study by Bilal et al, 2018 the mean age of females with diabetes was 49.05±10.08 years whereas for males was 52.76±11.31 years. The Wagner, and Texas university classification systems were the most extensively validated classification systems for diabetic foot ulcer outcome prediction. It was reported in the study by Sadriwala et al that Wagner grade was strongly associated with amputation as compared to other risk factors on multivariate analysis. Ulcers of Wagner grades 4 and 5 denote the presence of local or diffuse gangrene, which are usually due to a combination of ischemia and infection. In our study grade 4 and 5 ulcers were very strongly associated with amputation. Table 3 Shows Wagner’s grading distribution of patients at day 1 and after 3 months treatment, (p=0.034, significant, Paired proportion test) 28% improvement. Significant p values in comparison of study variables after 3 months at follow up measurements according to Wagner’s grading (Table 2, 9-10). Measurement of the ankle brachial index is a widely utilized test for the diagnosis of peripheral arterial insufficiency worldwide. The ABIs <0.9 and above 1.4 were significantly correlated with diabetic nephropathy, microalbuminuria, macro albuminuria and renal failure. In our study, ABI had values less than 0.9 in 52% at day one and 46% at three months, whereas ABI value of 0.9-1.3 was 48% and 54% at day 1 and month 3 respectively. No patients were noted to have ABI values greater than 1.3. In our study of the four patients who underwent major amputation, 3 patients had ABI of 0.6 and 1 patient’s ABI was 0.7.ABI (p=0.002) & Arterial Doppler findings (p=0.003) were seen in patients with Wagner’s grade 3, 4 and 5. Arterial Doppler studies of patients at day 1 and after 3 months of treatment (Table 4), p=0.003, significant, Paired proportion test, 10% Improvement (Table 4, 9-10). Hypoalbuminemia is a major contributing factor in wound healing. In our study, albumin levels of less than 3.5 at day one were seen in 42 (84%), between 3.5-5.5 in 8 (16%) and none had levels more than 5.5. Low albumin levels can be considered as a marker for lower extremity amputation. Patients with later stages of chronic kidney disease and advanced diabetic nephropathy have a greater risk of complications and mortality (Table 3, 9-10). The degree of renal impairment correlates strongly with the incidence and prevalence of DFU. In our study , 3 (6%) had a serum creatinine level less than 0.9 at day 1 and 6 (12%) had levels less than 0.9 at month 3. The number of patients who had serum creatinine levels between 0.9-1.3 was 24 (46%) and 26 (52%) at day 1 and month 3 respectively. (Tables 5, 9-10). Procalcitonin or a combination of procalcitonin and C-reactive proteins have been used as biomarkers of diabetic foot ulcer infection in several other studies. In our study, levels below 40 of C Reactive Protein were seen in 22 (44%) and 24 (48%) at day 1 and month 3 respectively. Higher levels of more than 40 were seen in 28 (56%) and 26 (52%) at day 1 and month 3 respectively (Table 10). In our study, low levels of HbA1c of <6.5 were not seen in any of the patients at presentation, while one (2%) of patients were able to achieve glycemic control at 3 months follow up. 34 (68%) of patients had HbA1c levels between 6.5-9 at presentation and the number increased to 38 (76%) at follow up of 3 months. Very high glycemic index of more than 9 was seen in 16 (32%) of patients on Day 1 and the number decreased to 11 (22%) at 3 months (Tables 6, 9-10). In our study, 39 (78%) and 40 (80%) of patients had serum total cholesterol levels below 200 at day 1 and month 3 respectively. The number of patients with serum cholesterol levels between 200-239 was comparable at day 1 and month 3 with 11 (22%) and 9 (18%) respectively. Higher levels of more than 239 were seen only in a single patient at 3 months follow up (Table 9-10). In our study, monophasic flow on arterial Doppler studies were seen in none at presentation while 7 (14%) showed at 3 months. 30 (60%) and 26 (52%) of patients had biphasic flow at day 1 and month 3 respectively. The number of patients showing tri phasic flow at day 1 and month 3 was 20 (40%) and 17 (34%) at day 1 and month 3 respectively. All the 4 (8%) patients who underwent major amputation had monophasic flow on Doppler studies at the time of surgery (Tables 4, 9-10).

**Limitations**

Small sample size and short duration of follow up period were the limitations of current study.

**CONCLUSION**

Diabetes mellitus is one of the leading causes for lower limb amputation. Clinical assessment of the diabetic foot ulcer and identification of the risk factors of non healing ulcers provides a key in the management of diabetic foot complications. Low serum Albumin, high CRP levels, High HbA1C levels, high urine PCR, high cholesterol levels, deranged renal function test are all predictive risk factors for lower extremity amputation. Multi-disciplinary approach is the most effective treatment strategy.

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