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# Outcomes and Predictors of Healing of Diabetic Foot Ulcer in a Diabetic Foot Center in Western Saudi Arabia: A Retrospective Study

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***Abstract:*** **A retrospective chart review of 147 patients registered at a Middle-Eastern diabetic foot center (DFC) to assess prevalence, outcomes and predictors of diabetic foot ulcer (DFU) healing. Data were collected for: 1) demographic data; 2) lifestyle and clinical factors, such as smoking, diabetes-related factors, and medical history; 3) first assessment and management of DFU, including location, date of onset, Wagner grade, accompanying neurovascular abnormalities (pulse, sensory loss, etc), associated factors (neuropathy, peripheral arterial disease, foot trauma), and management strategy; and 4) outcome data including healing/unhealing, recurrence, amputation and mortality. Appropriate statistical tests were used to explore factors of healing and binary logistic regression was used to analyze its predictors. Of the patients, 73.5% males, mean±SD age at first registration=53.90±16.43 years, mean±SD diabetes duration=11.33±7.53 years, with poor glycemic control in 33.3%. Foot ulcer was right located in 57.8%, with high Wagner grade (grade 4-5) in 32.2% cases. Healing was achieved in 64.6% of the patients, over 3.47±0.62 month duration from ulcer onset. Outcomes of healing included 20.0% of recurrence leading to 15.8% amputations, 2.1% of newly-onset ulcers and no mortality. Most significant predictors of healing included young age, urban setting, high educational level, fair-to-good glycemic control, absence of comorbidities, lower Wagner grade, and absence of neurovascular abnormalities. Healing of DFUs is achieved in 2 of 3 patients over a relatively short period with low recurrence and mortality rates. Low grade ulcers in young patients, who have good glycemic control and no significant comorbid conditions are more prone to healing.**

***Keywords:*** **Diabetic Foot; Complications; Ulcer; Healing; Recurrence.**

## 1. INTRODUCTION

Diabetes is one of the debilitating conditions and it is a major global concern of the 21st century afflicting 366 million people worldwide. Approximately, 80% of diabetic individuals are living in low and middle-income countries. It is anticipated that by 2030, the global epidemic of diabetes will increase to 552 million [1].Diabetic foot ulceration (DFU) is a concerning health problem in diabetes; defined as skin ulceration associated with neuropathy and or peripheral arterial disease of the lower limb. It is one of the most serious complications of diabetes with a prevalence that ranges from 4% to 10%; and which is highly prevalent in older patients. The lifetime risk of developing diabetic foot ulceration in diabetic patients is 15% [2].

The following are the 2 major classification systems for diabetic foot ulcers used globally for effective preventive and therapeutic measures [3]:

- Wagner classification: based on the depth or penetration of the wound, presence or absence of osteomyelitis or gangrene and the extent of tissue necrosis
- University of Texas: is based on the depth and penetration of wound, as well as presence or absence of infection and/or ischemia

Identification of the risk factors that contribute to DFU enables healthcare providers to tackle the condition with appropriate preventive and treatment measures. These measures reduce the need for amputation to a great extent and thus improve the quality of life of the patients [4].Increased duration of diabetes increases the risk of foot ulceration. Males, black race, smokers, aging, poor glycemic control, peripheral neuropathy, vascular insufficiency, low level of high density lipids, retinal or renal complications increases the risk of foot ulcers [3].The management of DFU is a major therapeutic challenge requiring active deployment of several preventive and curative strategies that should be offered in a timely, effective fashion at affordable cost. Increased awareness and improved communication among different specialties accelerate the decision making. Treating the patients with highest standard of care cost effectively, increased use of clinical guidelines reduces variability in clinical practice and improves the health care quality. The use of Critical pathway approach enhances the inpatient outcomes and decreases major amputations [5].

In the recent years, disease registries have turned out to be reliable sources in the management of chronic diseases such as diabetes. It is being effectively practiced in countries such as Denmark, Sweden, Singapore, Malaysia, Saudi Arabia, and Thailand to monitor diabetes [4].Systematic evaluation and appropriate categorization of foot ulcers is essential to provide appropriate treatment and continuously improve the management. Treatment aims to provide an early intervention to allow prompt healing of the lesion and prevent recurrence once it is healed. Multidisciplinary therapeutic options/programs that focus on education, prevention, regular foot examination, aggressive treatment, optimal use of therapeutic footwear demonstrated significant reduction in the incidence of lower extremity amputations [6].

Majority (80%) of the DFUs heal; while 15% remain active and to 24% lead to limb amputation in a span of 0.5 years to 1.5 years post first evaluation [2].Although, awareness and better technology emerged over the past few years in the management of diabetic foot, amputation rates remain unchanged and perhaps even increased in several regions.The primary challenge for the healthcare system today is managing the lower extremity of the diabetes clinically and cost effectively. Reduce the frequency of amputations, limiting the overall costs [5].

In this retrospective study, we assessed the outcomes of DFU in a single diabetic foot center, analyzed the prevalence and predictors of healing. We also explored subsequent follow-up events including recurrence, new ulcers,secondary amputation and death. We believe that this process leads to improving management of patients by defining controllable factors associated with favorable diabetic foot ulcer outcomes.

## 2. AIM & RATIONALE

This study assessed outcomes of diabetic foot ulcer in a single diabetic foot center and analyzed prevalence and predictors of healing. It also explored subsequent follow-up events including recurrence, new ulcers, secondary amputation and death. Such data will allow improving management of patients by defining controllable factors associated with favorable diabetic foot ulcer outcomes.

## 3. METHODS

A retrospective chart reviewwas carried outamong patients with diabetic foot complications (DFC0who were registered between January 2012 and December 2013and following for ≥ 3 month at the Diabetic Foot center,King Fahd Hospital, Jeddah, Kingdom of Saudi Arabia.Both patients known as being diabetic at first registration and those diagnosed with diabetes during follow up in the diabetic foot center were included. A data collection form was designed including 4 parts: 1) demographic and socioeconomic data such as gender, age at first registration, marital status, occupation, etc.; 2) lifestyle and clinical factors such as smoking status, body mass index (BMI), diabetes duration (from diagnosis to first diabetic foot center registration), quality of diabetes follow-up (regular/irregular), glycemic control (good/fair/poor), other medical history (hypertension, ischemic heart disease [IHD], nephropathy, etc.), and treatment (diet, insulin, oral anti-diabetic drugs [OAD]; 3) first assessment and management of diabetic foot, including location of the ulcer, date of onset, Wagner grade, accompanying signs (pulse, sensory loss, ankle reflex, infection), associated factors (diabetic neuropathy, peripheral arterial disease [PAD], foot trauma), and first management strategy (relief of pressure, debridement of necrotic tissue, special dressing, biological active implants [BAI], revascularization, anti-biotherapy and surgical drainage; and 4)

outcome data including patient and diabetic foot ulcer outcomes (healing/ unhealing), subsequent follow-up events including recurrence and ulcers at current and their management including amputation (degree: minor/major) and mortality.

***Statistical Analysis:***

Data was analyzed with the Statistical Package for Social Sciences version 21.0 for Windows (SPSS Inc., Chicago, IL, USA). Descriptive statistics were carried outto calculate frequencies and percentages for categorical variable and means (standard deviations [SD]) for numerical variables. Analytical statistics including chi-square test, Fisher's exact test and independent t-test, as appropriate, were used to analyze demographic, socioeconomic, lifestyle, clinical and ulcer-related factors as factors of ulcer healing. Binary logistic regression was carried out to analyze significant factors as predictors for healing. A p-value<0.050 was fixed for statistical significance.

## 4. RESULTS

***Demographic and socioeconomic characteristics of the population:***

The study included 147 patients with diabetic foot ulcer in which 73.5% were males with a mean±SD age of 53.90±16.43 years at first registration.Other demographic and socioeconomic characteristics showed that 24.5% of the patients were living in Bedouin village, 40.1% were of low economic class (< 5,000 SAR per month income), and 40.8% were poorly educated.The demographic and socioeconomic characteristics of the study population are presented in Table 1.

**Table 1: Demographic characteristics of the population (N=147)**

| Parameter | Category | Frequency | Percentage |
|---|---|---|---|
| Age at registration | Mean, SD (years) | 53.90 | 16.43 |
| Gender | Male | 108 | 73.5 |
| | Female | 39 | 26.5 |
| Nationality | Saudi | 119 | 81.0 |
| | Non-Saudi | 28 | 19.0 |
| Marital Status | Single | 13 | 8.8 |
| | Married | 112 | 76.3 |
| | Divorced | 8 | 5.4 |
| | Widowed | 14 | 9.5 |
| Number of children | Mean, SD | 4.55 | 3.11 |
| Accommodation | Urban | 36 | 24.5 |
| | Rural | 71 | 48.3 |
| | Bedouin | 36 | 24.5 |
| Cohabitation | Alone | 17 | 11.6 |
| | With family | 114 | 77.6 |
| | With friends | 2 | 1.4 |
| Monthly income (SAR) | <5,000 | 59 | 40.1 |
| | 5,000 – 10,000 | 49 | 33.3 |
| | 10,000 – 15,000 | 33 | 22.4 |
| | >15,000 | 6 | 4.1 |
| Occupation | Employed | 62 | 42.2 |
| | Housewife | 33 | 22.4 |
| | Unemployed | 23 | 15.6 |
| | Retired | 27 | 18.4 |
| Educational level | Illiterate | 30 | 20.4 |
| | Primary | 30 | 20.4 |
| | Secondary | 43 | 29.5 |
| | University | 39 | 26.5 |
| Some categories do not sum up to the total because of missing data; | | | |

***Lifestyle and clinical characteristics:***

The population included 48.3% active smokers, 85.7% who practiced no regular exercise and more than 75% of overweight or obese. Type II diabetes accounted for 79.6%, with irregular follow-up in 77.6% and poor glycemic control in 33.3%. Hypertension was the most frequent co-morbidity in 49.0% of the patients, followed by dyslipidaemia in 22.4% and visual impairment in 20.4% patients. Anti-diabetic treatment included diet in 94.6%, followed by OADs in 77.6% and insulin in 26.5%. The lifestyle and clinical characteristics are presented in Table 2.

**Table 2: Lifestyle and clinical characteristics of the population (N=147)**

| Parameter | Category | Frequency | Percentage |
|---|---|---|---|
| Smoking status | Non-smoker | 70 | 47.6 |
| | Smoker | 71 | 48.3 |
| | Ex-smoker | 6 | 4.1 |
| Regular exercise | Yes | 2 | 1.4 |
| | No | 126 | 85.7 |
| | Unknown | 17 | 11.6 |
| Weight | Mean, SD (Kg) | 85.30 | 20.60 |
| Height | Mean, SD (cm) | 166.62 | 11.47 |
| BMI | Underweight | 1 | 0.7 |
| | Normal weight | 26 | 17.7 |
| | Overweight | 44 | 29.9 |
| | Class I obesity | 44 | 29.9 |
| | Class II obesity | 16 | 10.9 |
| | Class III obesity | 5 | 3.4 |
| Diabetes type | Type I | 30 | 20.4 |
| | Type II | 117 | 79.6 |
| Diabetes duration | Mean, SD (years) | 11.33 | 7.53 |
| Diabetes follow-up quality | Regular | 19 | 12.9 |
| | Irregular | 114 | 77.6 |
| | Unknown | 14 | 9.5 |
| Glycemic control | Good | 8 | 5.4 |
| | Fair | 89 | 60.5 |
| | Poor | 49 | 33.3 |
| Comorbidity | Hypertension | 72 | 49.0 |
| | Dyslipidaemia | 33 | 22.4 |
| | Atherosclerosis | 11 | 7.5 |
| | IHD | 22 | 15.0 |
| | Stroke | 8 | 5.4 |
| | Visual impairment | 30 | 20.4 |
| | Nephropathy | 4 | 2.7 |
| | Surgery | 16 | 10.9 |
| Treatment | Diet | 139 | 94.6 |
| | Oral anti-diabetic | 114 | 77.6 |
| | Insulin | 39 | 26.5 |
| | Anti-cholesterol | 32 | 21.8 |
| | Platelet antiaggregant | 24 | 16.3 |
| | Antihypertensive | 59 | 40.1 |
| | Other | 3 | 2.1 |
| IHD: Ischemic heart disease; some categories do not sum up to the totalbecause of missing data; | | | |

***Assessment, management and outcomes of diabetic foot ulcer:***

Ulcer developed 11.32±7.48 years after diabetes diagnosis. It was the presenting symptom of diabetes in 4 patients who were diagnosed as diabetic in the DFC. Foot ulcer was unilateral in 95.9%; with high Wagner Grade (Grade 4-5) in 32.7% cases. On vascular examination, pulse was reduced or absent in 23.8% cases and a peripheral arterial disease (PAD) was present in 8.2%cases. On neurological examination, sensory loss was found in 38.8%, ankle reflex reduced or absent in 29.2% cases and an associated neuropathy was diagnosed in 32.7% cases. Signs of infections were present in 78.2% cases and trauma was present in 6.1% cases.

Treatment included pressure relief and debridement of necrotic tissue in almost 100% of patients; while revascularization, bioactive implants and surgical drainage interested 10.2%, 3.4% and 42.2% of patients, respectively. Anti-biotherapy was conducted in 95.9%cases. Assessment, management, and outcomes are presented in Table 3.

**Table 3: Assessment, management and outcomes of diabetic foot ulcer**

| Parameter | Category | Frequency | Percentage |
|---|---|---|---|
| Interval from diabetes diagnosis to ulcer onset | Mean, SD (years) [Range = -2.08; 29.83] | 11.32 | 7.48 |
| Ulcer location | Right limb | 85 | 57.8 |
| | Left limb | 56 | 38.1 |
| | Bilateral | 6 | 4.1 |
| Wagner grade | Grade 0 | 3 | 2.0 |
| | Grade 1 | 60 | 40.8 |
| | Grade 2 | 14 | 9.5 |
| | Grade 3 | 22 | 15.0 |
| | Grade 4 | 26 | 17.7 |
| | Grade 5 | 22 | 15.0 |
| Pulse | Present | 110 | 74.8 |
| | Absent | 35 | 23.8 |
| Sensation | No sensory loss | 88 | 59.9 |
| | Sensory less | 57 | 38.8 |
| Ankle reflexes | Normal | 98 | 66.7 |
| | Absent/reduced | 43 | 29.2 |
| Infection | No | 13 | 8.8 |
| | Yes | 115 | 78.2 |
| | Not documented | 19 | 12.9 |
| Associated factors | Neuropathy | 48 | 32.7 |
| | PAD | 12 | 8.2 |
| | Foot trauma | 9 | 6.1 |
| Therapeutic management | Pressure relief | 141 | 95.9 |
| | Debridement | 138 | 93.9 |
| | Special dressing | 69 | 46.9 |
| | Bioactive implants | 5 | 3.4 |
| | Revascularization | 15 | 10.2 |
| | Antibiotics | 141 | 95.9 |
| | Surgical drainage | 62 | 42.2 |
| Ulcer outcome | Healed | 95 | 64.6 |
| | Unhealed | 52 | 35.4 |
| Time from ulcer onset to healing | Mean, SD (months) | 3.47 | 0.62 |
| Amputation | Minor | 33 | 22.4 |
| | Major | 26 | 17.7 |
| | No amputation | 88 | 59.9 |
| Last patient status | Alive ulcer-free | 98 | 66.7 |
| | Alive with ulcer | 12 | 8.2 |
| | Dead | 5 | 3.4 |
| | Unknown | 32 | 21.8 |
| PAD: Peripheral arterial disease; some categories do not sum up to the total indicated in the column heading because of missing data; | | | |

Regarding outcomes, healing rate of 64.6% was experienced after 3.47±0.62 months following registration in diabetic foot center. Healed ulcers outcome was marked by 20.0% of recurrences and 2.1% new ulcer episodes. Recurrences were managed by amputation in 15 (15.8%) cases, (13 [13.7%] minor, 2 [2.1%] major amputations). Unhealed ulcers (N=52) underwent amputation in 84.6% (20 [38.5%] minor, 24 [46.2%] major) and were marked by 9.6% of mortality, all from major amputation group (Figure 1).

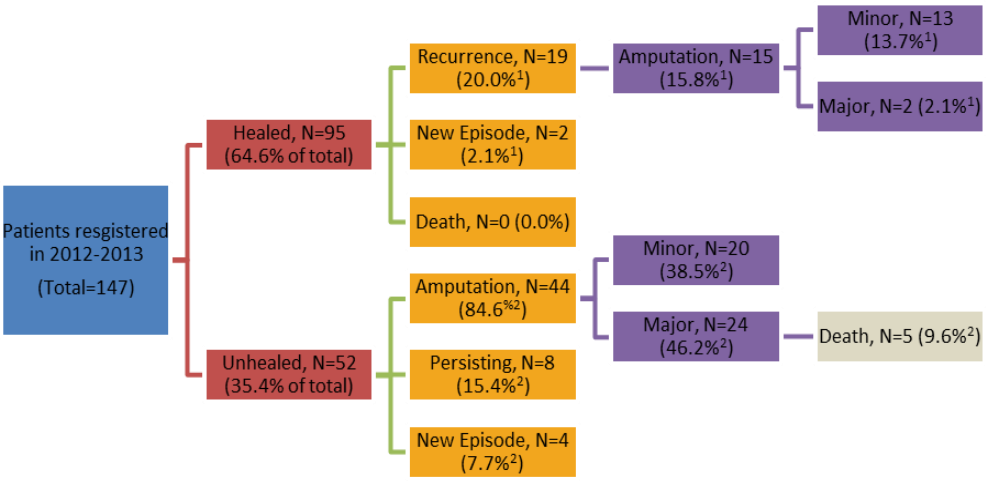


**Figure 1: Outcomes of healed and unhealed foot ulcer**

[1] Percentage calculated on number of healed; [2] calculated on number of unhealed ulcers.

***Factors associated with diabetic foot ulcer healing:***

Patients who achieved ulcer healing were younger (p=0.001), had less number of children (p=0.001), lived more frequently in rural or Bedouin towns (p=0.005) and had more frequently high income (p=0.001) and higher educational level (p<0.0001) by comparison to the unhealed (Table 4).

**Table 4: Demographic and socioeconomic factors associated with healing in diabetic foot ulcer**

| Factor | Category | Unhealed (N=52) | | Healed (N=95) | | p-value |
|---|---|---|---|---|---|---|
| | | F./Mean | %/SD | F./Mean | %/SD | |
| Age at first registration | Years | 61.94 | 13.86 | 49.50 | 16.11 | <.0001* |
| Number of children | | 5.78 | 3.20 | 2.89 | 2.87 | .001* |
| Gender | Male | 35 | 67.3 | 73 | 76.8 | .211 |
| | Female | 17 | 32.7 | 22 | 23.2 | |
| Nationality | Saudi | 40 | 78.4 | 78 | 82.1 | .591 |
| | Non-Saudi | 11 | 21.6 | 17 | 17.9 | |
| Marital status | Single | 2 | 3.8 | 11 | 11.7 | .136 |
| | Married | 40 | 76.9 | 71 | 75.5 | |
| | Divorced | 2 | 3.8 | 6 | 6.4 | |
| | Widowed | 8 | 15.4 | 6 | 6.4 | |
| Accommodation | Urban | 9 | 18.8 | 27 | 28.4 | .005* |
| | Rural | 19 | 39.6 | 52 | 54.7 | |
| | Bedouin | 20 | 41.7 | 16 | 16.8 | |
| Cohabitation | Alone | 7 | 15.2 | 10 | 11.5 | .499 |
| | With family | 39 | 84.8 | 75 | 86.2 | |
| | With friends | 0 | 0.0 | 2 | 2.3 | |
| Monthly income (SAR) | <5K | 30 | 57.7 | 29 | 30.5 | .001* |
| | 5K – 10K | 9 | 17.3 | 40 | 42.1 | |
| | 10K-15K | 13 | 25.0 | 20 | 21.1 | |
| | >15K | 0 | 0.0 | 6 | 6.3 | |
| Occupation | Employed | 20 | 40.0 | 42 | 44.2 | .504 |
| | Housewife | 15 | 30.0 | 18 | 18.9 | |
| | Unemployed | 7 | 14.0 | 16 | 16.8 | |
| | Retired | 8 | 16.0 | 19 | 20.0 | |
| Educational level | Illiterate | 22 | 44.0 | 8 | 8.7 | <.0001* |
| | Primary | 10 | 20.0 | 20 | 21.7 | |
| | Secondary | 11 | 22.0 | 32 | 34.8 | |
| | University | 7 | 14.0 | 32 | 34.8 | |
| * Statistically significant result (p-value<0.05); some values do not sum up to the total indicated in the column heading because of missing data; | | | | | | |

Regarding lifestyle and clinical factors, patients who achieved healing had shorter diabetes duration (mean±SD=10.71±6.91 years) by comparison of those who were unhealed (12.48±8.49); however, the result was not statistically significant (p=0.173). Significant factors of healing included good glycemic control (p=0.022), absence of comorbidities including hypertension (p<0.0001), dyslipidemia (p=0.0001), atherosclerosis (p=0.017), visual impairment (p=0.021) and nephropathy (p=0.014). Risk factors of unhealing included multiple pathology (p<0.0001), treatment with insulin (p=0.003) antihypertensive drugs (p=0.0005), anti-cholesterol (p=0.0001) and platelets antiaggregant treatments (p=0.0002) (Table 5).

**Table 5: Lifestyle and clinical factors associated with healing in diabetic foot ulcer**

| Factor | Category | Unhealed (N=52) | | Healed (N=95) | | p-value |
|---|---|---|---|---|---|---|
| | | F./Mean | %/SD | F./Mean | %/SD | |
| Weight | Kg | 82.90 | 23.58 | 86.61 | 18.78 | .298 |
| Height | Cm | 163.92 | 13.12 | 168.09 | 10.23 | .034* |
| BMI | Underweight | 0 | 0.0 | 1 | 1.1 | .202 |
| | Normal | 11 | 22.9 | 15 | 17.0 | |
| | Overweight | 13 | 27.1 | 31 | 35.2 | |
| | Class I obesity | 13 | 27.1 | 31 | 35.2 | |
| | Class II obesity | 7 | 14.6 | 9 | 10.2 | |
| | Class III obesity | 4 | 8.3 | 1 | 1.1 | |
| BMI (3 categories) | Normal or overweight | 11 | 22.9 | 16 | 18.2 | .588 |
| | Overweight | 13 | 27.1 | 31 | 35.2 | |
| | Obesity | 24 | 50.0 | 41 | 46.6 | |
| Smoking status | Non-smoker | 26 | 50.0 | 44 | 46.3 | .028* |
| | Current smoker | 21 | 40.4 | 50 | 52.6 | |
| | Ex-smoker | 5 | 9.6 | 1 | 1.1 | |
| Regular exercise | Yes | 1 | 1.9 | 1 | 1.1 | .777 |
| | No | 46 | 88.5 | 80 | 86.0 | |
| | Unknown | 5 | 9.6 | 12 | 12.9 | |
| Diabetes type | Type I | 12 | 23.1 | 18 | 18.9 | .553 |
| | Type II | 40 | 76.9 | 77 | 81.1 | |
| Diabetes duration | Years | 12.48 | 8.49 | 10.71 | 6.91 | .173 |
| Quality of diabetes follow-up | Regular | 3 | 5.8 | 16 | 16.8 | .072 [F] |
| | Irregular or not documented | 49 | 94.2 | 79 | 83.2 | |
| Glycemic control | Good | 2 | 3.8 | 6 | 6.4 | .022* |
| | Fair | 25 | 48.1 | 64 | 68.1 | |
| | Poor | 25 | 48.1 | 24 | 25.5 | |
| Glycemic control (2 categories) | Good or fair | 27 | 51.9 | 70 | 74.5 | .006* |
| | Poor | 25 | 48.1 | 24 | 25.5 | |
| Comorbidity | Hypertension | 38 | 73.1 | 34 | 35.8 | <.0001* |
| | Dyslipidaemia | 21 | 40.4 | 12 | 12.6 | .0001* |
| | Atherosclerosis | 8 | 15.4 | 3 | 3.2 | .017* [F] |
| | IHD | 11 | 21.2 | 11 | 11.6 | .120 |
| | Stroke | 4 | 7.7 | 4 | 4.2 | .454 |
| | Visual impairment | 16 | 30.8 | 14 | 14.7 | .021* |
| | Nephropathy | 4 | 7.7 | 0 | 0.0 | .014* |
| | Surgery | 9 | 17.6 | 7 | 7.7 | .072 |
| Number of comorbidities | None | 9 | 17.6 | 46 | 51.1 | <.0001* |
| | One | 10 | 19.6 | 27 | 30.0 | |
| | 2 or more | 32 | 62.7 | 17 | 18.9 | |
| Diabetes treatment | Diet | 47 | 90.4 | 92 | 96.8 | .131 [F] |
| | Oral anti-diabetic | 35 | 70.6 | 78 | 82.1 | .109 |
| | Insulin | 19 | 37.3 | 20 | 21.5 | .003* |
| | Anti-cholesterol | 21 | 41.2 | 11 | 11.6 | <.0001* |
| | Platelet antiaggregant | 16 | 30.8 | 8 | 8.4 | .0002* |
| | Antihypertensive | 31 | 59.6 | 28 | 29.5 | .0005* |

[F]: significance calculated using Fisher's exact test;
*statistically significant result (P<0.05); some values do not sum up to the total indicated in the column heading because of missing data;

Regarding ulcer-related factors, healing was associated with shorter ulcer evolution (time from ulcer to registration at DFC; p=0.030), lower Wagner grades (p<0.0001); absence of neurovascular abnormalities including pulse reduction or absence (p<0.0001), sensory loss (p<0.0001), ankle reflex reduction (p<0.0001), neuropathy (p<0.0001) and PAD (p=0.004). furthermore, patients with healed ulcers required less frequently implementation of specific therapeutic measures including special dressing (p<0.015), bioactive implants (p=0.002), revascularization (p<0.002) and surgical drainage (p<0.0001). Outcome analysis showed lower prevalence of amputations (p<0.0001) and major amputations (p<0.0001); and no mortality was recorded in healed patients (0.0%) versus 5 (9.6%) in unhealed ones, all having underwent major amputation. In addition, healing was associated with reduced follow-up duration (15.45±11.14 months) as compared with unhealing (25.61±16.77 months), p=0.012 (Table 6).

**Table 6: Ulcer-related factors associated with healing in diabetic foot ulcer**

| Factor | Category | Unhealed (N=52) | | Healed (N=95) | | p-value |
|---|---|---|---|---|---|---|
| | | F./Mean | %/SD | F./Mean | %/SD | |
| Time from diabetes diagnosis to ulcer onset (years) | | 12.37 | 8.51 | 10.74 | 6.83 | .209 |
| Time from ulcer onset to registration (month) | | 1.31 | 3.85 | -0.47 | 5.12 | .030* |
| Ulcer location | Right | 25 | 48.1 | 60 | 63.2 | .196 |
| | Left | 24 | 46.2 | 32 | 33.7 | |
| | Bilateral | 3 | 5.8 | 3 | 3.2 | |
| Wagner grade | Grade 0 | 0 | 0.0 | 3 | 3.2 | <.0001* |
| | Grade 1 | 1 | 1.9 | 59 | 62.1 | |
| | Grade 2 | 2 | 3.8 | 12 | 12.6 | |
| | Grade 3 | 15 | 28.8 | 7 | 7.4 | |
| | Grade 4 | 17 | 32.7 | 9 | 9.5 | |
| | Grade 5 | 17 | 32.7 | 5 | 5.3 | |
| Wagner (3 CAT) | Grade 0-1 | 1 | 1.9 | 62 | 65.3 | <.0001* |
| | Grade 2-3 | 17 | 32.7 | 19 | 20.0 | |
| | Grade 4-5 | 34 | 65.4 | 14 | 14.7 | |
| Other clinical signs | Pulse absence | 29 | 55.8 | 6 | 6.3 | <.0001* |
| | Sensory loss | 43 | 82.7 | 14 | 14.7 | <.0001* |
| | Reduced ankle reflex | 32 | 61.5 | 11 | 11.6 | <.0001* |
| | Infection | 44 | 84.6 | 71 | 74.7 | .091 |
| | Neuropathy | 34 | 65.4 | 14 | 14.7 | <.0001* |
| | PAD | 9 | 17.3 | 3 | 3.2 | .004* |
| | Foot trauma | 2 | 3.8 | 7 | 7.4 | .683 |
| Ulcer management | Pressure relief | 49 | 94.2 | 92 | 96.8 | .666 |
| | Debridement | 50 | 98.0 | 88 | 93.6 | .422 |
| | Special dressing | 30 | 57.7 | 39 | 41.1 | .015* |
| | Bioactive implants | 4 | 7.8 | 1 | 1.1 | .002* |
| | Revascularization | 11 | 22.0 | 4 | 4.3 | .002* |
| | Antibiotics | 50 | 96.2 | 91 | 95.8 | 1.000 |
| | Surgical drainage | 41 | 85.4 | 21 | 23.1 | <.0001* |
| Outcomes | New episode | 4 | 7.7 | 2 | 2.1 | .186 |
| | Amputation | 44 | 84.6 | 15 | 15.8 | <.0001* |
| | *Minor* | *20* | *38.5* | *13* | *13.7* | <.0001* |
| | *Major* | *24* | *46.2* | *2* | *2.1* | |
| | Death | 5 | 9.6 | 0 | 0.0 | <.0001* |
| Follow-up time | Mean, SD (months) | 25.62 | 16.77 | 15.45 | 11.14 | .012* |
| PAD: Peripheral Arterial Disease; * statistically significant result (p<0.05) | | | | | | |

***Predictors for healing in diabetic foot ulcer:***

Most significant demographic and socioeconomic predictors of healing among diabetic patients with foot ulcer included age (OR=0.94; p<0.0001), living in Bedouin town (OR=0.27; p=0.010), high income and high educational level. Clinical predictors included poor glycemic control (OR=2.7; p=0.006); absence of comorbid hypertension (OR= 0.21; p<0.0001), dyslipidemia (OR=0.21; p=0.0002), and atherosclerosis (OR=0.18; p=0.015); or existence of 2 or more comorbidities (OR=0.10; p<0.0001). Treatment with insulin (p=0.044), anti-cholesterol (p=0.0001), platelets antiaggregant (p=0.001) and antihypertensive drugs (p=0.0005) were associated with 0.46, 0.19, 0.21, and 0.28 odds-ratios of healings, respectively. Ulcer-related predictors of healing included lower Wagner grade (grade 0-1>2-3>4-5); absence of associated

neurovascular abnormalities including pulse absence or reduction, sensory loss, ankle reflex reduction, neuropathy and PAD; and no recourse to specific therapeutic measures including special dressing, revascularization and surgical drainage. Results of all explored predictors are presented as OR [95%CI] with significance level for each predictor category in Table 7.

**Table 7: Predictors of healing among patients with diabetic foot ulcer (univariate binary logistic regression)**

| Predictor | Category | Or | 95%CI | | p-value |
|---|---|---|---|---|---|
| | | | Min. | Max. | |
| **Demographic and socio-economicfactors** | | | | | |
| Age at first registration | (years) | 0.94 | 0.92 | 0.97 | <.0001* |
| Number of children | | 0.81 | 0.71 | 0.93 | .002* |
| Accommodation | Urban | *Ref* | - | - | .007* |
| | Rural | 0.91 | 0.36 | 2.29 | .845 |
| | Bedouin | 0.27 | 0.10 | 0.73 | .010* |
| Income | <5K | *Ref* | - | - | .010* |
| | 5K-10K | 4.60 | 1.90 | 11.41 | .001* |
| | 10K-15K | 1.59 | 0.67 | 3.78 | .929 |
| | >15K | I | I | I | .999 |
| Educational level | Illiterate | *Ref* | - | - | <.0001* |
| | Primary | 5.50 | 1.81 | 16.68 | .003* |
| | Secondary | 8.00 | 2.77 | 23.10 | .0001* |
| | University | 12.57 | 3.98 | 39.72 | <.0001* |
| **Lifestyle and clinical factors** | | | | | |
| Smoking status | Non-smoker | *Ref* | - | - | .075 |
| | Current smoker | 1.41 | 0.70 | 2.84 | .341 |
| | Ex-smoker | 0.12 | 0.01 | 1.07 | .057 |
| Diabetes duration | (years) | 0.97 | 0.93 | 1.01 | .173 |
| Glycemic control | Good or fair | 2.70 | 1.32 | 5.52 | .006* |
| | Poor | *Ref* | 0.18 | - | - |
| Comorbidity‡ | Hypertension | 0.21 | 0.10 | 0.43 | <.0001* |
| | Dyslipidaemia | 0.21 | 0.09 | 0.49 | .0002* |
| | Atherosclerosis | 0.18 | 0.05 | 0.72 | .015* |
| | Nephropathy | I | I | I | I |
| Number of comorbidities | None | *Ref* | - | - | <.0001* |
| | One | 0.53 | 0.19 | 1.46 | .219 |
| | 2 or more | 0.10 | 0.04 | 0.26 | <.0001* |
| Treatment | Insulin | 0.46 | 0.22 | 0.98 | .044* |
| | Anticholesterol | 0.19 | 0.08 | 0.43 | .0001* |
| | Platelet-antiaggregant | 0.21 | 0.08 | 0.53 | .001* |
| | Antihypertensive | 0.28 | 0.14 | 0.58 | .0005* |
| **Ulcer-related factor** | | | | | |
| Interval Dx to ulcer onset | (years) | 0.97 | 0.93 | 1.02 | .208 |
| Wagner grade | Grade 0-1 | *Ref* | - | - | <.0001* |
| | Grade 2-3 | 0.02 | 0.00 | 0.14 | .0002* |
| | Grade 4-5 | 0.01 | 0.00 | 0.05 | <.0001* |
| Other clinical signs | Pulse absence | 0.05 | 0.02 | 0.13 | <.0001* |
| | Sensory loss | 0.03 | 0.01 | 0.08 | <.0001* |
| | Reduced ankle reflex | 0.07 | 0.03 | 0.16 | <.001* |
| | Neuropathy | 0.09 | 0.04 | 0.21 | <.001* |
| | PAD | 0.16 | 0.04 | 0.61 | .007* |
| Ulcer management | Special dressing | 0.46 | 0.23 | .933 | .031* |
| | Bioactive implants | 0.12 | 0.01 | 1.09 | .059 |
| | Revascularization | 0.15 | 0.05 | 0.51 | .002* |
| | Surgical drainage | 0.05 | 0.02 | 0.14 | <.0001* |

OR: Odds-ratio; 95%CI confidence interval; *ref*: reference category;
***** statistically significant result ($p<0.05$); I: invalid result; ‡ presence versus absence of the given comorbidity; IHD: ischemic heart disease; Dx: diabetes diagnosis; PAD: peripheral arterial disease;

## 5. DISCUSSION

Diabetic ulcers, one of the complications of diabetes have gained significance due to socio-economic burden it imposes both on the patient and health care system. Management of DFUs remains a major therapeutic challenge. There is an urgent need to review predictors for ulcer development and healing, strategies and treatments to achieve the goals and reduce the burden of care in an efficient and cost-effective manner. The present study analyzed prevalence, outcomes and predictors of healing in DFU followed up in a DFC. It showed numerous significant findings, which are discussed and analyzed as follows:

Healing rate, which was achieved over a mean period of 3.47±0.62 month from ulcer onset, was 64.6% of the cases. This is poorer as compared to that observed in other centers; such as in a foot care clinic in Nottingham, which reported 91.7% of healing rate without amputation [7], or another Australian center reporting 89% of healing [8]. Another recent study by Formosa et al reported relatively lower rate of 77% of healing and 23% of amputations in a period of 1 year [9].

In this study, the development of ulcer was 11.32±7.48 years after diabetes diagnosis. Several other studies have shown similar duration for the development of DFUs. Fatah et al., in a retrospective study reported that DFU were developed in subjects who were suffering from diabetes for more than a decade. These patients showed approximately 17-fold increases in the prevalence of DFU compared with diabetic patients with less than 10 years duration [10]. Similarly, Reiber et al, showed a 6-fold increase in the risk of DFU in patients with diabetes for more than 20 years [11]. The mean duration of diabetes was greater than 10 years in patients who developed DFUs as per the findings in the Seattle Diabetic Foot Study by Bokyo and his colleagues [12].

Time data was not sufficiently available to accurately calculate healing time and to analyze time predictors of DFU outcomes; as it was primarily defined amongst the study objectives. We can however deduce from analysis of other variables that average healing time was around 3 months. This is comparable to what was reported in another study conducted by Jeffcoate et al who reported the median time from presentation to the clinic to healing to be 78 (7–364) days and 79 (7–364) [13].

Old and lowly educated patients living in rural or Bedouin areas with low income were disadvantaged for healing, by comparison to young, educated patients living in urban areas and having good income level. This is in agreement with several other studies; as advancing age is generally identified as a poor predictor of healing in DFUs [14, 15]. Regarding education, low educational level is probably associated to low awareness and health education, both resulting in patients with poor prevention and already advanced pathology at diagnosis. It has been demonstrated that approximately 50% of DFU cases can be prevented by effective education, which is considered to be the cornerstone to prevent DFUs [16]. Further, with higher education, routine foot care and attention to footwear, incidence of ulcers and amputations can be reduced by 44-85%; hence, foot care advice and knowledge about risk factors is very important for healing of DFUs [3]. In Saudi Arabia, there is insufficient knowledge and awareness among patients and general population about diabetes and diabetes complications including DFUs. Ahmed et al, found that 90% of screened Saudi diabetic patients had poor knowledge about their disease and 96.3% had poor awareness about its control; which was correlated with poor education. Lack of education and unawareness leads to negligence of diabetic foot complications and poor compliance with the preventive and therapeutic measures [17].

Our study results showed that good glycemic control, absence of comorbidities such as hypertension, dyslipidemia, atherosclerosis, visual impairment, and nephropathy are key clinical factors of healing. Risk factors of unhealing included multiple pathological conditions, treatment with insulin, antihypertensive, anti-cholesterol, and platelets antiaggregant treatments. Formosa et al who reported 77% of healing rate demonstrated that glycemic control was considered to be one of the significant predictors of healing, and that patients with lower HbA1c had significantly faster healing rates than their counterparts [9]. Registered Nurses Association of Ontario (RNAO) expert panel has recognized poor glycemic control and heart disease as poor predictors of healing DFUs and PAD can prolong wound healing [14]. AlGoblan AS, et al prospective analytical study concluded that BMI and HbA1c levels were strongly associated with DFUs healing in the diabetic patients, where higher BMI and elevated HbA1c were associated with poor prognosis [18]. Other clinical factors associated with healing failure included the presence of neurovascular signs such as reduced ankle reflex, pulse absence or an adjacent peripheral arterial disease. All these factors indicating multiple pathology and advanced diabetes with more severe macrovascular and microvascular complications are known risk factors of DFU and poor wound healing. Ghanassia et al., in a 6.5 year follow-up long-term study assessed the outcome and functional status of subjects hospitalized for diabetic foot ulcers and demonstrated that smoking, popliteal stenosis, and renal impairment were

considered to be univariate predictors of healing failure [19]. Hypertension, a treatable risk factor is strongly linked to macrovascular and microvascular complications and it significantly increases the risk for amputation. On the other hand, improved control of hypertension is essential to decrease the DFUs complications [14]. Brownrigg, et al. in a meta-analysis study revealed that the prevalence of coronary artery disease, cerebrovascular disease, hypertension and hypercholesterolemia is particularly high in patients with DFU [20]. The observations in this meta-analysis study and our study results are well aligned with respect to the cardiovascular comorbidity and diabetes macro- and microvascular complications and their impact on healing DFUs. Comparably, the EURODIALE study indicated that heart failure, the inability to stand or walk without help, end-stage renal disease, peripheral neuropathy and PAD are independent predictors of non-healing. PAD is present in approximately half of the patients with foot ulcers and is considered to be one of the significant predictor of DFUs outcome. The outcome of patients without PAD was relatively favorable with 84% of healing with or without minor amputation, 2% of major amputation and 3% died. Loss of sensation was also associated with poorer outcomes [15]. Thus, focused foot examination on the presence of peripheral neuropathy, PAD and abnormal foot anatomy can predict patients at high risk of developing DFU. In addition, aggressive cardiovascular risk management in diabetes is proved to provide better health benefits as per Steno-2 study [21].The Seattle Diabetic Foot Study concluded that medical history of the patient might help in assessing the chances for the development of DFU and may help in accurately targeting persons at high risk of healing failure. These will help the healthcare providers to recommend appropriate preventive and therapeutic interventions on a timely manner. Commonly available clinical information has the ability to predict the development of DFU over a period of 1 to 5 years of duration with a high degree of accuracy [20].

Treatment intensity in the group with unhealed DFUs showed that they were more frequently on insulin, in addition to treatments for other pathologies including antihypertensive drugs, anti-cholesterol and platelets antiaggregant treatments, which is indirectly indicative of the multiple pathology in the unhealed group by comparison to healers. Another study that compared diabetic patients with to those without DFU reported that the percentage of oral hypoglycemic agents' users was higher among non-affected cases when compared with diabetic foot cases who were frequent insulin users [4].

Majority of the identified ulcer-related predictors of healing or healing failure are similar to data from other studies. However, wound characteristics were not collected appropriately; which constituted another limitation of the study that prevented from analyzing healing in correlation with wound characteristics. In the EURODIALE Study, larger ulcer size, along with presence of peripheral neuropathy and PAD at baseline were demonstrated to be significant predictors of non-healing [15]. According to a predictive wound model designed by wound healing society, the variables that significantly predicted healing included wound age (duration in days), wound size, Wagner grade, and number of concurrent wounds of any etiology; in addition to other factors such as evidence of infection, patient age, renal dialysis, renal transplant, and peripheral vascular disease [22]. Formosa et al, in their 1-year follow-up study concluded that wound characteristics such as ulcer stage, biofilm presence, and depth of ulcer were more predictive of ulcer healing [9]. Further, early changing parameters can be used to predict healing as shown by a prospective trial conducted by Sheehan et al. who demonstrated that a 50% reduction in wound surface area in a month is a good predictor of complete wound healing at 12 weeks [23].

Aggressive therapeutic measures including special dressing, revascularization and surgical drainage of ulcer were shown to predict unhealing in our study. This opposes results from other studies showing better healing in patients treated with aggressive treatments. A literature review article published in world journal of diabetes revealed the main clinical components of management that can ensure successful and rapid healing of DFUs as debridement, advanced dressing, offloading, surgery, and advanced therapies. These clinical steps must be used in order to reduce the complications of DFUs [16]. By confrontation to these observations, our results may suggest a low concordance between management strategy and risk stratification where appropriate therapeutic measures may be initiated after attempting simple measures in high risk patients. Early implementation of aggressive measures such as bioactive implants, revascularization and surgical drainage should be considered in high-risk patients; while simple measures can be attempted in low risk patients as first-line therapy.

We observed 20% cases of recurrence among healer; however, data was insufficient to calculate ulcer-free days and analyze risk factors of recurrence. Ghanassia et al reported that primary reason of recurrence among patients who experienced ulcer healing was found to be the treatment with insulin before admission and it was the only predictor of ulcer recurrence, in addition to advanced age which was found to be one of the treatment failure predictor in achieving global therapeutic success [19].

Healing was associated with approximately 10-month reduction of follow-up duration in DFC, which probably represents important difference in the patient's quality of life and induces significant cost savings.

This study highlighted unsatisfactory DFU healing rate in our study population, which is likely to be attributable to low education among our patients and lack of awareness regarding diabetes and diabetes complication, all resulting in poor glycemic control and delayed detection of diabetes complications, and probably associating poor compliance with preventive and therapeutic procedures. Other findings suggested that an improvement in therapeutic indication should be considered in appropriateness with risk stratification including overall patient's pathological condition and wound characteristics. Thus, systemic, accurate and comprehensive clinical assessment of patient and wound characteristics at first admission and close monitoring of the early wound change can help to identify the barriers for the control of DFUs and implement the appropriate therapeutic strategy to enhance the healing and prevent poor outcomes including recurrence, amputation and death. Diabetic patients followed in primary healthcare should benefit from early multidisciplinary management with focus on awareness, prevention and regular foot examination; to allow timely referral to specialized centers at early stage of diabetic foot complication.

## 6. LIMITATIONS

As specified before, because of retrospective design, several variables such as wound characteristics, healing time and ulcer-free days could not be collected appropriately; which prevented from carrying out deeper analysis principally Kaplan-Mayer analysis and time predictors of healing, recurrence and newly-onset ulcers.

## 7. CONCLUSION

Two out of three diabetic foot ulcers heal after specialized management in the participating diabetic foot center. Healing is associated to low recurrence and amputation rates and null mortality. It is more likely to be achieved in young patients who are highly educated, living in urban setting, and having good glycemic control; and it is less likely to be achieved in patients with other comorbidities such as hypertension and atherosclerosis or multiple pathologies, and those having high Wagner grade ulcer with associated neurovascular signs.

The detection of these predictive factors through accurate, comprehensive clinical assessment of patients at first admission plays vital role in identifying the barriers for the control of DFUs and defining appropriate therapeutic strategy to enhance the healing and prevent poor outcomes including recurrence, amputation and death.

The role of primary healthcare should be integrated in the multidisciplinary approach; focusing on awareness, prevention and regular foot examination to initiate specialized follow-up, at early stage of diabetic foot complication.

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