

# Characteristics Predicting Foot Ulceration Outcomes in the Diabetic Foot

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## ABSTRACT

Diabetic foot complications are common amongst people living with diabetes. Foot ulcerations are one of the most feared complications for both people with diabetes and health care providers due to their negative impact on lives resulting in overall poor prognosis of the disease, leading to long periods of hospitalization and substantial health care costs. The literature suggests that diabetes foot complications including ulcerations could be ameliorated and even prevented if this condition is managed correctly. However, although several countries and organizations, such as the World Health Organization, International Working Group on the Diabetic Foot and the International Diabetes Federation, have set guidelines to define standards of care using evidence-based interventions to reduce the rate of amputations by up to 50%, the literature reports variations of care. Data on outcomes and determinants of outcomes in individuals living with diabetic foot ulcerations is either limited or varied with several patient and ulcer characteristics being reported

as possible factors which could influence ulcer healing. The ability to predict whether a diabetic foot ulcer is following versus not following a healing trajectory could dramatically alter patient outcomes. The aim of this chapter is to report results from a recent study evaluating patient and ulcer characteristics which could possibly predict wound healing in patients living with diabetes. Although large clinical randomized studies on characteristics predicting foot ulceration outcomes in the diabetic foot are limited, this chapter provides evidence on potential predictors. Findings reported in this chapter have important implications for both clinical practice and future research. Findings suggest that prediction of outcome may be helpful for healthcare professionals in individualizing and optimizing clinical assessment and management of patients. Identification of determinants of outcome could result in improved health outcomes, improved quality of life and lesser diabetes related foot complications.

**Keywords:** Diabetic foot ulcers; Amputations; Healing; Outcome

## INTRODUCTION

The prevalence of diabetes is increasing worldwide and although previously, it was considered to be a disease of the rich class, today, due to a high calorie intake of rich food and decreased physical exercise amongst all populations, it is also belonging to lower socio-economic strata.

It has been estimated that 4-10% of people with type 2 diabetes develop a diabetes related foot complication such as foot ulceration [1]. Diabetic foot complications are common amongst people living with diabetes when compared to other related diabetes complications. This is of concern for both people with diabetes and healthcare providers, with episodes of ulceration strongly associated with lower-extremity amputations, reduced quality of life, long periods of hospitalization and substantial health care costs [2]. It has been estimated that an amputation is performed on a person living with diabetes somewhere in the world every thirty seconds [3]. It has been reported that 24.4% of the total health care expenditure among diabetic population is related to diabetic foot complications and the total cost of treating diabetic foot complications is approaching 11 billion USD in America and 456 million USD in the United Kingdom [4].

Diabetic foot ulcerations can take weeks or months to heal and can sometimes not heal at all [5]. Owing to poor healing results, many patients will need to be admitted to hospital for inpatient treatment [6]. Non-healing ulcerations can result in diabetes foot complications such as local infection, gangrene and amputation of the limb [7]. This emphasizes the importance of ensuring continuous research in order to identify the best methods of management to ensure high quality and effective treatment.

The aim of the research presented in this chapter is to obtain prospective data over a period of one year on foot ulcer outcome [healing vs non healing] and determinants of these outcomes in patients living with diabetes in this specific Maltese population. Results were later compared to results of similar studies conducted abroad to determine whether determinants of outcome

are congruent or otherwise amongst different countries. Such information will undoubtedly go a long way towards alleviating to some extent, the burden and costs related to diabetic foot complications in countries who share similar cultures. A key reason for identifying factors that prolong healing is to modify these factors and improve outcomes with the aim of decreasing diabetic foot complications.

## **MATERIAL AND METHODS**

### **Subject Selection**

Individuals were recruited from the Diabetes Podiatry Clinic in a local general hospital. A convenience sample of 101 subjects was recruited for this investigation. A priori power analysis was calculated. This study was approved by the University Research Ethics Committee and all participants provided informed consent before any data collection. All investigations were carried out in accordance with the principles of the Declaration of Helsinki as revised in 2000. Participants eligible for this study were subjects, aged >18 years, living with diabetes according to the World Health Organization diagnostic criteria. Patients who presented for the first time with new foot ulceration over a 1-year period at an outpatient hospital clinic were recruited into this study. Participants were excluded if they presented with venous ulcers, had a history of foot ulceration or amputation, underwent revascularization procedures of the lower limb or were either unable to participate in the study due to cognitive impairments or showed unwillingness to participate and follow study protocol.

### **Methodological Rigor**

A prospective observational study was conducted. The clinical tools used during this research were based on validated and previously published methods following a thorough review of the literature on international guidelines and recommendations. A database was constructed to record all the information.

### **Methods**

Hundred and one subjects were recruited in this prospective observational study and were followed and treated until healing was achieved or up to a maximum period of 12 months according to a standardized protocol described below based on the International Consensus on the Diabetic Foot [8]. Two participants died during the study period leaving the number of recruited subjects that of 99. Assessment of the neurological and vascular status, regular wound debridement, diagnosis and treatment of infection, dressings of ulcers and offloading was conducted.

The participants were asked to visit the diabetes foot clinic once every 4 weeks following recruitment and were followed for a maximum period of 12 months. The primary outcome measure was ulcer healing. Healing was defined as complete epithelialization without discharge and without amputation. Time to healing was calculated from the date of first clinic attendance to the date at which the foot ulcer was first confirmed as healed in the clinic. Those who had an ulcer

related amputation (major/minor) or died during the year of study were censored at the date of amputation or death. Specific patient and ulcer characteristics were selected to cover a wide range of previously identified predictive factors for ulcer healing as detailed below.

## Patient Characteristics

After informed consent, patients' characteristics were gathered using a self-designed data collection sheet structured for the purpose of gathering data from participants including gender, age, type and duration of diabetes and weight. In addition to the latter, details concerning date of diagnoses of diabetes, medication regimen for diabetes and other medications, renal function, heart failure, history of coronary artery bypass graft (**CABG**), hypertension, hypercholesterolemia and neurological disorders were recorded from patients' history notes. Additional information including vision, symptoms of Peripheral Arterial Disease [**PAD**] such as intermittent claudication and rest pain, and smoking habits were recorded. Participants were also asked if they are able to stand or walk without help. Any foot disorders, the type of shoe and offloading devices were also recorded. The type of wound dressing and their ability to change the dressing was noted. Participants' present occupation was also recorded. Clinical measurements including HBA1c, Creatinine level and estimated Glomerular Filtration Rate [**GFR**] were measured every 4 months as part of the patients' routine clinic inside the Diabetes and Endocrinology Centre. All patients underwent a standardised ulcer examination every four weeks up to a period of one year using the Perfusion, Extent/size, Depth/tissue loss, Infection and Sensation [**PEDIS**] classification tool [9].

## Ulcer Characteristics

In order to classify patients in this study an examination of the foot following the Perfusion, Extent/size, Depth/tissue loss, Infection and Sensation (**PEDIS**) systems as recommended by the International Consensus on the Diabetic Foot [8] was conducted. Foot ulcerations were classified according to 5 categories including perfusion, extent, depth, infection and sensation. The testing modalities and examination methods were carried out by the same investigator to ensure uniformity. Testing was performed at the outpatient's clinic. Room temperature was kept at 21 to 23 degrees Celsius (68 to 75 F) during the assessments to avoid vasoconstriction of digital arteries from the cold. The screening process involved review of the patient's medical history and a lower-extremity physical examination. Individual assessments took approximately 45 minutes.

## Peripheral sensory neuropathy

The 10-g Semmes-Weinstein monofilaments were used to identify peripheral sensory neuropathy. The five-point test was used. The plantar aspect of the hallux and third digit together with the 1st, 3rd and 5th metatarsal heads were used for testing. With the eyes closed, the patient related to the investigator when he or she could feel the monofilament. Participants with triphasic waveforms, normal ABPI's (0.9 – 1.2) and who were unable to feel the 10gram monofilament on any of the 5 points were considered as neuropathic.

## Peripheral arterial disease

Peripheral Arterial Disease [PAD] was assessed using the documentation of history of intermittent claudication, rest pain and palpation of peripheral pulses. Palpation of pulses was conducted by an experienced clinician. Dorsalis pedis and posterior tibial pulses were recorded. Cyanosis, cold feet, skin thinning and hair anomalies were also recorded. Claudication was evaluated from information supplied by the patient with regard to exercise-induced calf, thigh and/or buttock pain.

Measurement of Ankle Brachial Pressure Index [ABPI] was performed using a portable hand held Doppler and blood pressure cuffs. Apart from ABPI assessment quantitative pedal waveform analysis was obtained from all recruited subjects utilizing the continuous wave Doppler. The Doppler waveforms and the measurement of the ankle brachial pressure index were obtained using the 'Huntleigh® Dopplex Assist vascular package (Cardiff, UK)' as the principal study tool. The Huntleigh® hand held continuous wave Doppler with an 8MHz probe, part of the Dopplex Assist vascular package, was used to measure the waveforms of the dorsalis pedis and the posterior tibial arteries. The probe was held steadily on the anatomical artery location at an angle between 45 to 60 degrees against the flow of arterial blood. Interpretation of arterial pressure waveforms results was based on standards from the literature. Waveforms were classified as triphasic, biphasic, monophasic discontinuous and monophasic continuous. The triphasic and biphasic waveforms were considered as normal, whereas the monophasic discontinuous and monophasic continuous waveforms were interpreted as abnormal and indicative of PAD. Measurements were carried out after a 5-minute rest in supine position with the upper body as flat as possible. Patients were also asked to undo all tight clothing around the waist and the arm. The Huntleigh® Dopplex Assist Series was used to measure the resting ABPI. The series used for this study included an electric pump which deflates the pressure cuffs, requiring the investigator to simply press a button. An optimum Doppler signal is achieved at an angle of 45 to 60 degrees. When measured, the systolic blood pressures are automatically saved onto the system's software with the saved results then used to calculate the ABPI ratios by the system.

A blood pressure cuff was applied to the arm [to measure the brachial systolic pressure] and the ankle [to measure the dorsalis pedis and posterior tibial pressures] to determine the ankle pressure. The cuff was inflated to occlude the arterial pressure. The systolic pressure was obtained by listening and noting the pressure on the manometer. The systolic pressure was noted and the higher values of the brachial and the ankle pressures were used to calculate the ABPI. Values were interpreted according to the criteria proposed by the American Heart Association and the American Diabetes Association [10]. ABPI calculations were interpreted as 0.9– 1.29 normal, lower-extremity vascular diseases was defined an ankle brachial index < 0.90 in either foot. An ABPI of >1.3 was considered significantly elevated and indicative of vascular calcification.

## Extent

The extent was recorded using the acetate method, which involved tracing the circumference of the wound onto a two layered 1mm<sup>2</sup> preprinted acetate tracing. The contact layer was discarded and the area of the wound was calculated by counting each square that is more than half within the border of the wound as 1mm<sup>2</sup> [11].

## Depth

Depth was measured by inserting a sterile probe into the deepest part of the wound, placed a gloved forefinger at the level of the surrounding skin, and measured the length of probe within the wound against a paper ruler.

## Infection

Infection was diagnosed in cases when two or more of the following signs were present: frank purulence, local warmth, erythema, lymphangitis, oedema, pain, fever and foul smell.

Ulcer site was documented and categorised as toe, metatarsophalangeal joint, mid or hind foot. Other ulcer characteristics that were recorded include whether the ulcer base was wet, moist or dry. The presence of slough, necrotic/eschar, granulating or epithelialising tissue, as well as the presence of biofilm was recorded. Biofilm was diagnosed when a greyish thick, slimy barrier was observed [12]. An attempt was also made to estimate the time in days which elapsed between ulcer onset and first attendance to the clinic.

Ulcers were also categorised according to their type. In patients whose ABPI was found to be <0.9mmHg and whose peripheral sensation was poor, these were diagnosed as having a neuro-ischaemic ulcer. The typical characteristics of a neuro-ischaemic ulcer were; a base of sparse pale granulation tissue, a yellowish closely adherent slough and were usually found on the margins of the foot, especially on the medial surface of the first metatarsophalangeal joint and over the lateral aspect of the fifth metatarsophalangeal joint [13]. In patients with an ABPI of 0.9mmHg to 1.3mmHg but presenting with poor peripheral sensation, these were diagnosed as having a neuropathic ulcer. The characteristics of a typical neuropathic ulcer were; a punched out appearance, the presence of granulation tissue, a sloughy appearance, being surrounded by hyperkeratosis and the presence of whitish, macerated, moist tissue [14]. Neuropathic ulcers were usually found on the plantar aspect of the foot under the metatarsal heads or the apices of digits and heels. Patients whose ABPI was <0.9mmHg but their peripheral sensation was good, these were diagnosed as having an ischaemic ulcer. If a patient happened to have multiple ulcers, the first, or the clinically most important (highest grades for area, depth or arteriopathy at presentation), was selected at the index lesion for the study. Ulcer area and depth, presence of infection and state of ulcer base were all recorded every 4 weeks for a maximum period of 12 months.

The above mentioned independent variables were chosen after a thorough literature search on factors that could influence diabetic foot ulcer healing as discussed in the introduction.

## STATISTICAL ANALYSIS

All data was recorded on a spreadsheet designed in Microsoft Excel to group together the information required for interpretation of the results. Statistical analyses were carried using the SPSS version 14. The One- way ANOVA [Analysis of Variance] or the Chi-Square test were performed for all potential predictor variables of wound healing with values presented with the respective 95% CI. Secondly, all significant predictors found in the above univariate analyses were entered simultaneously in a logistic regression analysis model. This model yielded a set of variables that can be regarded as independent predictors of foot ulcer outcome as described in the results below.

## RESULTS

### Patient demographics and ulcer characteristics

A total of 99 subjects, including 69 males and 30 females presenting with a new foot ulcer were recruited in this study. Six participants were living with type 1 diabetes and 94 subjects had type2 diabetes. The mean age of the study group ( $\pm$ SD) and duration of diabetes was  $62.8 \pm 9.5$  and  $14.8 \pm 9.0$  years, respectively. Seventy per cent of ulcers were neuropathic, 25.3% neuroischaemic, 4% ischaemic in nature. Most ulcers presented with slough (59.6%), necrotic/eschar (6.1%), granulating (30.3%), epithelialising (4%). Furthermore 25.2% presented with biofilm. Additionally, 36.4% of all ulcers showed clinical evidence of infection at presentation.

### Outcome

The primary outcome measure was ulcer healing. Those who had an amputation were classified as unhealed. At the termination of the study, 77% of ulcers had healed/resolved completely and 23% resulted in lower limb amputation over a maximum period of one year.

### Patient Characteristics and Foot Ulcer Outcome – Univariate Analysis

Results demonstrated no significant predictors of wound healing amongst patient characteristics recorded, however upon further statistical analysis when HbA1c was associated with the time to healing it proved to be a significant predictor ( $p=0.009$ ).

### Ulcer Characteristics and Foot Ulcer Outcome

At baseline ulcer area of each group was as follows: healed ulcer group [ $n=77$ ]  $51.82 \pm 22.36$ ; amputation group [ $n=23$ ]  $49.17 \pm 30.21$ . There was no significant difference in ulcer area amongst the two group ( $P=0.904$ ).

In the healed ulcer group 72.4% were neuropathic, 23.7% were neuroischaemic and 3.9% were ischaemic. Amongst the amputated group 65.2% were neuropathic, 30.4% were neuroischaemic and 4.3% were ischaemic. The mean duration between estimated ulcer onset and first assessment was  $12.68 \pm 2.84$  for the resolved group and  $18.26 \pm 6.87$  for the amputated group [ $p=0.081$ ].

In terms of ulcer characteristics, toes were most affected in both groups [resolved group n=44 vs amputated group n=20]. Other commonly affected areas included MPJ's, mid foot and hind foot.

## Logistic Regression Model and Odds Ratio

All identified potential predictors from the univariate analysis including ulcer stage, ulcer depth, ulcer base, presence of infection, presence of biofilm and Doppler waveforms all measured at time 0 [at the beginning of the study] were further analysed using a logistic regression analysis model to identify independent predictors of outcome. These predictors were selected either because their p values were less than the 0.05 level of significance or were slightly above the 0.05 criterion when conducting univariate analysis. The six predictor logistic regression model explains 48% of the total variation in the outcomes using the Nagelkerke Pseudo R-square value. This model identifies three significant independent predictors including ulcer stage at time 0 [p=0.003], presence of biofilm [p=0.020] at time 0 and depth at time 0 [p=0.028]. Doppler waveforms, infection and ulcer base were not found to be significant.

The odds ratio for depth of wound at time 0 [1.176], indicates that for every 1mm increase in depth the odds of amputation rather than resolved increases by 17.6%. The odds ratio for presence of biofilm at time 0 (1.990) indicates that the odds of amputation is 1.99 times larger in the presence of biofilm at time 0 compared to its absence. The odds ratio for the presence of slough, necrosis and eschar [ulcer stage], at time 0 (7.035) indicates that the odds of amputation is 7.035 times greater in the presence of slough, necrosis and eschar when compared to the granulating and epithelialising stage at time 0.

## DISCUSSION

The study reported in this chapter [15] aimed to identify which patient and/or ulcer characteristics could determine or predict ulcer healing in people living with diabetes. Prediction of outcome allows health care professionals dealing with the high risk foot to individualize and optimize clinical assessment, treatment and advice given to patients with the aim to minimize diabetes foot complications in this vulnerable population. Given the large number of diabetic foot complications and amputations reported annually globally, it is important to identify modifiable predictors that could determine foot ulcer outcome. This in turn could only result in identifying new therapeutic targets which could possibly result in reducing health care costs and improved quality of life in patients presenting with such complications. Our study concludes [15] that ulcer characteristics are more predictive of wound healing than patient characteristics. Three potential variables including ulcer stage, presence of biofilm and ulcer depth were identified as important factors related to wound healing. These findings are congruent with other similar studies conducted abroad. In an observational study conducted by Yesil et al [16], the authors examined the possibility of predicting the foot ulcer outcome of patients living with diabetes. Yesil et al [16], concluded that ulcers of Wagner grades 4 and 5 which denote the presence of local or diffused gangrene were very strongly associated with amputation (p<0.001). These results are



very similar to the findings of the current study, were participants who presented with necroses/eschar at baseline (time 0), all underwent amputation (26.1%). The authors also confirmed that ulcer depth is a significant predictor of wound healing. The authors concluded that deep wounds are at a higher risk of amputation ( $p < 0.001$ ). In a recent prospective study conducted by Zubair et al [17] risk factors for amputation amongst patients living with diabetic foot ulceration were investigated. This study highlighted that the presence of biofilm is a significant predictor of lower limb amputation (Odds Ratio: 4.52).

Although unlike other studies, our study demonstrated that the baseline HbA1c reading was not a significant predictor of foot ulcer outcome [ $p = 0.603$ , resolved vs amputated], however upon further statistical analyses, when HbA1c was compared to the time taken for complete ulcer healing in the healed group [ $n = 77$ ], it proved to be significant [ $p = 0.009$ ]. The literature identifies many physiological factors as contributors to poor wound healing in patients living with diabetes including decreased or impaired keratinocyte and fibroblast migration and proliferation, cytokine and growth factor function and angiogenic response and response to infection amongst others [18], however these factors are all dependant on the levels of glucose in the blood [19]. Suboptimal HbA1c levels may hold prognostic significance in patients presenting with diabetes ulcerations. Findings from our study are congruent to those of another retrospective study conducted by Christman et al [20] where the authors concluded that individuals with a lower HbA1c had significantly faster healing rates [ $p = 0.027$ ].

As highlighted by the EURODIALE Study [21], since outcome data on people living with diabetic foot ulcerations is scarce, and furthermore studies evaluating outcome have reported different patient and/or ulcer characteristics which could predict wound healing in this specific population living with diabetes, evidence supports the need for further studies in this field to explore the relationship between patient baseline characteristics and ulcer characteristics and their outcome on ulcer healing to add to the current body of knowledge. The identification and modification of predictive risk factors could mean less long-term complications such as amputations and less expenditure from health budgets, whilst at the same time improve patients' quality of life.

## CONCLUSION

After 1 year of follow-up, ulcer characteristics were more predictive of ulcer healing than patient characteristics in this study group. The factors influencing healing are ulcer stage, presence of biofilm and ulcer depth. These findings have important implications for clinical practice especially in an out-patient setting. Early recognition of factors which influence healing together with appropriate management of ulcerations is essential for a successful outcome [36]. Prediction of outcome may be helpful for healthcare professionals in individualizing and optimizing clinical assessment and management of patients. Identification of determinants of outcome could result in improved health outcomes, improved quality of life and lesser diabetes related foot complications.

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