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Determinants of wound healing in patients hospitalized for diabetic foot ulcer: results from the MEDFUN study

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Objective. The high amputation rates from diabetic foot ulcer (DFU) in Nigeria and prolonged hospitalization due to poor wound healing is a source of concern. Furthermore, factors that affect wound healing of DFUs have not yet been well studied in Nigeria, whereas knowing these factors could improve DFU outcomes. Therefore, the objective of this study was to determine the factors that are associated with the wound healing in patients hospitalized for DFU.

Methods. The Multi-Center Evaluation of Diabetic Foot Ulcer in Nigeria (MEDFUN) was an observational study involving 336 diabetic patients hospitalized for DFU and managed by a multidisciplinary team until discharge or death. Demographic, clinical, and biochemical characteristics were documented. Test statistics used were chi square, t-test, univariate, and multivariate logistic regression. The study endpoints were ulcer healing, LEA, duration of hospitalization, and mortality. Here we present data on wound healing.

Results. The mean ± SD age was 55.9±12.5 years. Univariate predictors of wound healing were ulcer duration more than 1 month prior to hospitalization ($p<0.001$), peripheral arterial disease (PAD) ($p<0.001$), foot gangrene ($p<0.001$), Ulcer grade ≥3 ($p=0.002$), proteinuria ($p=0.005$), anemia ($p=0.009$), renal impairment ($p=0.021$), glycated hemoglobin ≥7% (0.012), and osteomyelitis ($p<0.001$). On multivariate regression, osteomyelitis was the strongest independent predictor of wound healing after adjusting for all other variables (OR 0.035; 95% CI 0.004–0.332). This was followed by PAD (OR 0.093; 95% CI 0.028–0.311), ulcer duration >1 month (OR 0.109; 95% CI 0.030–0.395), anemia (OR 0.179; 95% CI 0.056–0.571).

Conclusion. Presence of osteomyelitis, duration of ulcer greater than 1 month, PAD, Wagner grade 3 or higher, proteinuria, presence of gangrene, anemia, renal impairment, and HbA1c ≥7% were the significant predictors of wound healing in patients hospitalized for DFU. Early identification and prompt attention to these factors in a diabetic foot wound might significantly improve healing and reduce adverse outcomes such as amputation and death.

Key words: wound healing, predictors, diabetes, foot ulcer, MEDFUN, Nigeria

Diabetes mellitus (DM) is a chronic metabolic disorder that presents with various complications, especially if it is not properly managed. It is the leading cause of non-traumatic lower extremity amputation (LEA). People with diabetes have from 15 to 40 times higher risk of LEA than those without diabetes (CDC 2006). It is estimated that about 12% of all hospitalized patients with diabetes in Africa have foot ulceration (Mbanya and Sobngwi 2003). Research indicates that patients with diabetic foot ulcers encounter

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stigma, loss of social role, social isolation, and unemployment (Harrington et al. 2000). Diabetic foot ulcer (DFU) is a costly and debilitating disease with potentially severe consequences (Iraj et al. 2013). According to reports, treatment outcome for DFU is generally poor even in centers with well-established multidisciplinary diabetic foot care units, with poor DFU healing rates observed in some studies (Margolis et al. 1999). Treatment outcome for DFU is determined by several factors. These include: the pathogenesis of the ulcer (neuropathic vs. ischemic), glycemic control (usually poor in many cases), surgical interventions, wound care techniques employed, and the presence or absence of infections (Elgzyriet al. 2013; Piaggesi et al. 1998; Yesil et al. 2009). In our environment, socioeconomic and sociocultural factors such as poverty, poor hygiene, walking barefooted, and ignorance are also issues to contend with (Piaggesi et al. 1998; Adeleye 2005; Out et al. 2013).

The increased incidence of DFU in patients with DM results from the interaction of several pathogenic factors that include neuropathy, abnormal foot biomechanics, peripheral arterial disease, and poor wound healing (Alvin 2005). Peripheral sensory neuropathy interferes with normal protective mechanisms and allows the patient to sustain major or repeated minor trauma to the foot, often without knowledge of the injury (Alvin 2005). Disordered proprioception causes abnormal weight bearing while walking followed by subsequent formation of callus or ulceration (Alvin 2005). Both motor and sensory neuropathy lead to abnormal foot muscle mechanics and structural changes in the foot (hammer toe, claw toe deformity, prominent metatarsal heads, Charcot joint). Autonomic neuropathy results in anhidrotic and altered superficial blood flow in the foot, which promote drying of the skin and fissure formation (Alvin 2005). Peripheral arterial disease and poor wound healing impede resolution of minor breaks in the skin, allowing them to enlarge and to become infected. Wound healing is impaired in patients with diabetes and has been attributed to both macro- and microvascular disease leading to tissue hypoxia, peripheral neuropathy, and abnormal cellular and inflammatory pathways predisposing to infection in foot ulcers (Alvin 2005).

Effective management of the diabetic foot needs not focus only on the outcome of DFU but also on the limbs and the patient. This implies that greater emphasis on prevention should be made. The principles of foot ulcer management include ensuring adequate vascularization to aid healing, infection control, and adequate wound care (pressure offloading and surgical debridement) (Young et al. 2016).

The high amputation rates from DFU in Nigeria and prolonged hospitalization due to poor wound healing is a source of concern; Furthermore, factors that affect wound healing of DFUs have not yet been well studied in Nigeria and knowing these factors could improve DFU outcomes, hence the objective of this study.

The objective of the study was to determine the factors that are associated with the wound healing in patients hospitalized for DFU.

Methods

The current research was part of the Multi-Center Evaluation of Diabetic Foot Ulcer in Nigeria (MEDFUN), a prospective observational study of patients with type 1 or type 2 diabetes who were hospitalized for DFU in six tertiary healthcare institutions in Nigeria, between March 2016 and April 2017. These centers include Enugu State University Teaching Hospital (ESUTH), Lagos State University Teaching Hospital (LASUTH), Aminu Kano Teaching Hospital, Ahmadu Bello University Teaching Hospital Zaria, Federal Medical Center Keffi and Federal Medical Center Umuahia. Approval of the study protocol was obtained from the local Research and Ethics committee of each of the hospitals, while verbal informed consent was obtained from each patient prior to recruitment. Pregnant women, subjects with diabetes other than types 1 and 2, and those with wounds limited to above the ankle joints were excluded.

Detailed methodology of the MEDFUN study has been published (Ugwu et al. 2019). In summary, relevant socio-demographic and diabetes-related information such as gender, age, occupation, cigarette smoking status, diabetes type and duration were obtained and documented. Distinction between type 1 and type 2 DM was made clinically as follows: subjects who reported dependence on insulin for diabetes control since the time of diagnosis were classified as type 1 diabetes (T1DM) while those who had been controlled on oral anti-diabetic drugs (OAD) with or without insulin were adjudged to have type 2 diabetes mellitus (T2DM).

Patients were interviewed on knowledge of proper foot care practices. History of development and progression of ulcer including mechanism of ulceration, site of ulcer, duration of ulcer and prior ulcer treatment methods were assessed. Clinical wound infection was determined according to the Interna-

tional Working Group on Diabetes Foot (IWGDF) guideline (Bakker et al. 2016) by the presence of any two of the following: periwound edema, tenderness, differential warmth, wound exudates and foul smell. Commonly known risk factors for DFU were also evaluated, including history of previous DFU, barefoot walking, improper foot wear, visual impairment, foot deformity, peripheral neuropathy and PAD. Peripheral neuropathy was diagnosed by loss of pressure perception to Semmes-Weinstein 10g monofilament test or diminished vibration sense using the 128Hz tuning fork. Peripheral artery disease was diagnosed on the presence of diminution or absence of dorsalis pedis and/or posterior tibial artery pulsations on manual palpation, ankle brachial index (ABI) < 0.9 or significant arterial narrowing (>50%) on Doppler ultrasonography of the lower limbs. The severity of ulcer was graded using the Wagner's grading system (Wagner 1987; Lavery et al. 1996).

Relevant laboratory and imaging studies were performed for each subject including urine protein, glycated hemoglobin (HbA1c), and lipid profile, plain radiograph of the foot and Doppler ultrasonography of both lower limbs. Co-morbid complications including anemia, kidney disease were explored and documented. Every patient received appropriate multi-disciplinary care and was followed up until discharge or death. Outcome variables of interest included predictors of ulcer healing. Wound healing was defined as complete re-epithelialization at 24 weeks. Descriptive data of the entire study population have been published (Ugwu et al. 2019). We hereby present results of sub-analysis of data related to wound healing.

For the current sub-analysis, we performed unadjusted associations between demographic, clinical, and laboratory variables and wound healing using the Chi-Square statistics for categorical variables and t-test for continuous variables. To identify independent predictors of amputation, we first performed univariate logistic regressions for each variable with wound healing as the dependent outcome, and calculated variable odds ratios (ORs) and 95% confidence intervals (CI). All the variables that emerged as significant predictors at this univariate level of analysis were then simultaneously entered into a multivariate regression model that was reduced using a backward selection method. Model reliability was determined by the Hosmer and Lemeshow test of goodness of fit. Analysis was done with the Statistical Package for Social Sciences (IBM version 23.0; SPSS Inc., Chicago, IL, USA). All tests were 2 tailed and $p<0.05$ was considered significant.

Results

Out of the 336 patients that participated in this study, the mean ± SD age was 55.9±12.5 years. Neuro-ischemic ulcers patients with neuro-ischemic ulcers had the highest mean ± SD age of 59.8±12.4, while patients with unclassifiable ulcers had the lowest mean ± SD age. The mean ± SD duration of DM was 8.5±5.7 years, with ischemic ulcers and unclassifiable groups having the longest (10.2±6.0) and shortest (4.7±3.2) mean ± SD duration of diabetes, respectively. Majority of the subjects with (96.1%) had type 2 diabetes. Majority of the subjects were males (55.1%), while current smokers constituted 5.1% of the subjects. In terms of ulcer grade, 79.2% had advanced ulcer (Wagner grade ≥3). Gangrene was present in 53% of all groups, while ischemic ulcer subjects had the largest percentage of patients presenting with gangrene (66.7%). Glycemic control was generally poor with mean HbA1c of 9.6±1.9%. The average healing time of the ulcers was 51.7±17.6 days while neuro-ischemic ulcers had the longest healing time of 62.4±13.1 days. Furthermore, neuro-ischemic ulcers had the least number of healed ulcers (10.4%). About one third of the study population underwent amputation and out of this number, 75.6% had major amputation. The mean duration of hospitalization was 50.8±28.0 days, while the mortality rate was 20.5% (Table 1).

Table 2 shows the demographic and clinical factors associated with wound healing. There was no association between participants' age and wound healing ($p>0.05$). Similarly, there was no association between the subjects age, smoking status and wound healing ($p>0.05$, $p>0.05$ respectively). A greater majority of patients with type 1 DM experienced poor wound healing (46.2%) when compared with patients with type 2 DM (26.7%), although this was not statistically significant ($p=0.154$). Subjects with ulcers longer than 1-month duration were 18.7% less likely to heal (OR 0.187; $p<0.001$) The result shows that patients with Wagner grade less than 3 were four times more likely to heal than those with Wagner 3 and above and this was statistically significant (OR 4.087; $p<0.005$).

Table 3 shows the univariate predictors of wound healing. Patients with proteinuria were 0.459 times less likely to have satisfactory wound healing and this was statistically significant (OR 0.459; 95% CI 0.268–0.787; $p=0.005$). Patients with HbA1c <7% were 4 times more likely to have satisfactory wound healing (OR 3.904; 95% CI 1.345–11.33; $p=0.012$). Similarly, patients with presence of radiologic features of osteomyelitis were 0.07 times less likely to have satisfac-

Table 1
Demographic and clinical characteristics of the subjects by ulcer type.

Variable	Neuropathic	Ischemic	Neuro-ischemic	Unclassifiable	Overall
N	125	42	135	34	336
Age (years)	53.4±11.9	56.3±8.7	59.8±12.4	49.7±14.1	55.9±12.5
Gender (Male)	67 (53.6)	26 (61.9)	76 (56.3)	16 (47.1)	185 (55.1%)
Smoking (Current)	6 (4.8)	2 (4.8)	6 (4.4)	3 (8.8)	17 (5.1)
DM Type (type 2)	117 (93.6)	42 (100.0)	134 (99.3)	30 (88.2)	323 (96.1%)
DM Duration (years)	8.1±5.6	10.2±6.0	9.3±5.8	4.7±3.2	8.5 ± 5.7
Onset (Spontaneous)	80 (64.0)	29 (69.0)	92 (68.1)	20 (58.8)	221 (65.8)
Ulcer duration (years)[a]	30 (28)	42 (25)	44 (25)	30 (20)	38.5 (26)
Advanced Ulcer (Wagner grade ≥3)	93 (74.4)	34 (81.0)	118 (87.4)	21 (61.8)	266 (79.2%)
Wound infection	97 (77.6)	33 (78.6)	103 (76.3)	25 (73.5)	258 (76.8%)
Presence of gangrene	55 (44.0)	28 (66.7)	87 (64.4)	8 (23.5)	178 (53.0)
History of previous foot Ulcer	31 (24.8)	12 (28.6)	43 (31.9)	10 (29.4)	96 (28.6%)
HbA1c (%)	9.3±1.9	9.7±1.8	10.0±2.1	9.0±1.6	9.6±1.9
Healed Ulcers	56 (44.8)	6 (14.3)	14 (10.4)	19 (55.9)	95 (28.3)
Healing Time (days)	52.2±18.1	55.3±13.4	62.4±13.1	41.0±15.4	51.7±17.6
Amputation	26 (20.8)	21 (50.0)	66 (48.9)	6 (17.6)	119 (35.4%)
Major Amputation (n=119)	15 (57.7)	14 (66.7)	57 (86.4)	4 (66.7)	90 (75.6%)
Duration of Hospitalization (days)	52.5±24.0	46.1±29.0	51.8±32.6	45.9±19.6	50.8±28.0
Mortality	17 (14.4)	12 (30.0)	35 (31.5)	5 (15.6)	69 (20.5%)

tory wound healing (OR 0.07; 95% CI 0.025–0.198; p<0.001). Subjects with anemia were 0.525 times less likely to have significant wound healing (p=0.009). Patients with renal impairment were 0.444 times less likely to achieve wound healing (OR 0.44; 95% CI 0.219–0.884; p=0.021). The association between lipid levels and outcome of diabetic foot ulcer healing was not statistically significant as there were no significant differences between patients with normal values of total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides and those with abnormal values (p=0.703, 0.296, 0.090, 0.598).

Table 4 shows the multivariate predictors of wound healing. In this study, osteomyelitis was the strongest independent predictor of wound healing after adjusting for all other variables (adjusted OR 0.035; 95% CI 0.004–0.332). Subjects with DFU and osteomyelitis were 0.035 times less likely to heal. This was followed by PAD (adjusted OR 0.093), ulcer duration >1 month (adjusted OR 0.109), anemia (adjusted OR 0.179).

Discussion

Totally 336 patients participated in this study. The mean ± SD age was 55.9±12.5 years, showing that our study population is largely middle aged, which is in keeping with findings from other studies (Atosona and Larbie 2019; Djibril et al. 2018; Saleem et al. 2017). About 96% of the patients in this study had type 2 diabetes, similar to findings from other studies, which reported type 2 diabetes as the commonest type of diabetes (Mehmood et al. 2008; Pemayun and Naibaho 2017). About four out of every five patients in this study (79.3%) had ulcer grade (Wagner) ≥3, while gangrene was present in 53% of patients, which is in keeping with reports from other studies (Djibril et al. 2018). This finding highlights the worrisome challenges in managing DFU in our environment as most of these patients would have experimented with unorthodox treatment modalities, which unfortunately would have failed them before presenting to the doctor. Moreover, the belief that DFU is a spiri-

Table 2
Demographic and clinical factors associated with wound healing.

Variable	Satisfactory healing		p-value	OR	95% C.I for OR
	Yes n (%)	No n (%)			
Age group					
≥65	68 (77.3)	20 (22.7)	0.114	0.536	0.247–1.163
45–64	142 (71.0)	58 (29.0)	0.386	0.745	0.383–1.449
<45	31 (64.6)	17 (35.4)			
Gender					
Male	132 (71.4)	53 (28.6)	0.866	1.042	0.646–1.680
Female	109 (72.2)	42 (27.8)			
Cigarette Smoking					
Current smoker	9 (52.9)	8 (47.1)	0.104	2.268	0.845–6.089
Ex-smoker	33 (78.6)	9 (21.4)	0.363	0.696	0.318–1.521
Never smoked	199 (71.8)	78 (28.2)			
Hypertension					
Present	138 (72.3)	53 (27.7)	0.806	0.942	0.584–1.520
Absent	103 (71.0)	42 (29.0)			
Type of diabetes					
Type 1	7 (53.8)	6 (46.2)	0.154	2.254	0.737–6.889
Type 2	234 (72.4)	89 (27.6)			
Duration of diabetes					
≤10 years	176 (70.4)	74 (29.6)	0.358	1.301	0.742–2.283
>10 years	65 (75.6)	21 (24.4)			
Duration of ulcer					
>1 month	195 (82.3)	42 (17.7)	<0.001	0.187	0.111–0.313
≤1 month	46 (46.5)	53 (53.5)			
Neuropathy					
Present	190 (72.5)	72 (27.5)	0.544	0.840	0.479 – 1.474
Absent	51 (68.9)	23 (31.1)			
Peripheral artery disease					
Present	156 (88.6)	20 (11.4)	<0.001	0.145	0.083–0.254
Absent	85 (53.1)	75 (46.9)			
Foot Gangrene					
Present	80 (50.6)	78 (49.4)	<0.001	0.108	0.060–0.195
Absent	161 (90.4)	17 (9.6)			
Ulcer grade (Wagner)					
<3	9 (40.9)	13 (59.1)	0.002	4.087	1.684–9.916
≥3	232 (75.9)	82 (26.1)			
Wound infection					
Present	190 (73.6)	68 (26.4)	0.157	0.676	0.393–1.163
Absent	51 (65.4)	27 (34.6)			

tually inflicted illness also drives these patients to seek spiritual solutions before presenting albeit late to their doctor.

Glycemic control in our study, as reflected by the mean HbA1c of 9.6±1.9%, was generally poor, which is not surprising. Reasons attributable to this may range from lack of access to medical care, poor drug adherence, and poverty. These could limit patient's capacity to purchase drugs and insulin, especially where health insurance is not very effective and efficient unlike what is obtainable in developed countries. Similar findings have been reported in a study carried out in Indonesia where more than 81% of the study population had HbA1c of at least 8%, with a mean HbA1c of 11.2% (Mehmood et al. 2008). Other studies have reported similar high values (Pemayun and Naibaho 2017; Hartemann-Heutier et al. 2002; Ozkara et al. 2008).

Pemayun and Naibaho (2017) in an Indonesian study have reported a mean duration of diabetes to be 6.4 years which is lower than the finding of 8.5 years in our study, although lower than the >10 years reported in a Pakistan study (Mehmood et al. 2008). The average healing time of the ulcers were 51.7 days while neuro-ischemic ulcers had the longest healing time of 62.4 days which is lower than findings by Zimny et al. (2002) who have reported an average healing time of 77.9 days and 123.4 days for neuro-

Table 3
Univariate predictors of wound healing.

Variable	Satisfactory healing		p-value	OR	95% CI for OR
	Yes n (%)	No n (%)			
Proteinuria					
Present	98 (81.0)	23 (19.0)	0.005	0.459	0.268–0.787
Absent	135 (66.2)	69 (33.8)			
Glycated hemoglobin					
<7%	6 (40.0)	9 (60.0)	0.012	3.904	1.345–11.330
≥7%	203 (72.2)	78 (27.8)			
Radiologic osteomyelitis					
Present	87 (95.0)	4 (4.4)	<0.001	0.070	0.025–0.198
Absent	134 (60.4)	88 (39.6)			
Anemia					
Present	140 (77.8)	40 (22.2)	0.009	0.525	0.324–0.849
Absent	101 (64.7)	55 (35.3)			
Renal impairment					
Present	55 (83.3)	11 (16.7)	0.021	0.440	0.219–0.884
Absent	185 (68.8)	84 (31.2)			
Total cholesterol					
Abnormal	98 (70.5)	41 (29.5)	0.703	0.905	0.542–1.512
Normal	93 (68.4)	43 (31.6)			
LDL Cholesterol					
Abnormal	113 (72.0)	44 (28.0)	0.296	0.759	0.453–1.272
Normal	78 (66.1)	40 (33.9)			
HDL Cholesterol					
Abnormal	138 (74.2)	48 (25.8)	0.090	0.639	0.381–1.073
Normal	68 (64.8)	37 (35.2)			
Triglycerides					
Abnormal	75 (71.4)	30 (28.6)	0.598	0.867	0.509–1.476
Normal	117 (68.4)	54 (31.6)			

Table 4
Multivariate predictors of wound healing.

	B	Sig.	Adjusted OR	95% CI for OR	
				Lower	Upper
Spontaneous ulcers	0.023	0.969	1.023	0.316	3.310
Ulcer duration >1 month	–2.215	0.001	0.109	0.030	0.395
Peripheral artery disease	–2.371	0.000	0.093	0.028	0.311
Poor glycemic control	1.770	0.108	5.872	0.679	50.740
Osteomyelitis	–3.339	0.003	0.035	0.004	0.332
Anemia	–1.720	0.004	0.179	0.056	0.571

ischemic ulcers. This finding is not surprising considering the fact that wound healing in patients with diabetes can be difficult due to combination of factors like hyperglycemia, chronic inflammation, micro and macro-circulatory dysfunction, hypoxia, autonomic and sensory neuropathy, and impaired neuropeptide signaling (Baltzis et al. 2014). In general, wound tends to heal more slowly and progress more quickly in diabetes. This worrisome statistic justifies the need to deploy early preventive measures in patients with diabetes like education on care of the foot, ensuring good glycemic control, adherence to clinic visits and compliance with medications. This is in a bid to avoid the humongous cost of prolonged hospital admission in these patients. Furthermore, neuro-ischemic ulcers had the least number of healed ulcers (10.4%).

Our study further showed that presence of proteinuria was strongly associated with poor wound healing ($p<0.05$) in the univariate regression. This finding is similar to a report from Germany where Apelqvist et al. (1992) have observed that proteinuria was more common in patients with poor wound healing as signified by amputation than patients with primary wound healing and this difference was significant. Thewjitcharoen et al. (2014) in a Thailand study have reported that presence of renal impairment is a risk factor for poor wound healing, though they used serum creatinine as a marker of renal function. Patients with renal dysfunction due to diabetes kidney disease are prone to impairments in glycolysis in neutrophils. In addition, once accumulated, uremic toxins lead to phagocytic dysfunction. Therefore, these patients are disposed to developing impaired infection control (Choi et al. 2017).

Our data showed that presence of anemia was strongly associated with poor wound healing ($p<0.05$) and this finding is in keeping with reports from Israel (Feldman-Idov et al. 2013) and China (Chuan et al. 2016). Anemia is known to be associated with hypoxemia, which leads to decreased oxygen supply to tissues and this will ultimately result to poor wound healing.

When adjusted for confounding factors, multivariate regression shows that ulcers lasting more than one-month duration was strongly associated with poor wound healing ($p<0.05$). This is in keeping with report by Lavery et al. (2006) who observed that ulcer lasting longer than 30 days of duration was associated with a three-fold increase in wound infection. This may be attributable to the fact that ulcer lasting for a longer duration increases the likelihood of wound infection with resultant tissue necrosis and increased chance of poor wound healing. This finding is a reflection of the impact of late presentation on the clinical outcome of these patients. In several instances, patients have been known to resort to self-denial or may attribute their ulcers to spiritual causes and thus believing that only prayers will be the needed solution. Besides, some patients resort to self-medications, which in the long run, prolongs the duration of ulcers and worsen their clinical state.

Poor wound healing was largely observed in patients with ulcer grade (Wagner) >3 and those with PAD and when adjusted for confounding factors in the multivariate regression analysis, PAD was strongly associated with poor wound healing. Pemayum et al. (2015) and Marston (2006) in their study have noted that presence of PAD and advanced ulcer grades were poor predictive factors of wound healing. This finding highlights the need for preventive action by all stakeholders especially in resource poor settings like ours. There should be a need for vascular assessment using Doppler instruments, neuropathy assessment using 10g monofilaments so that such cases can be detected early. More so, there is limited number of vascular surgeons in our locale and even where they are available, equipments for revascularization procedures may be lacking. Data from our study

reported osteomyelitis as a poor predictor of wound healing ($p<0.05$), which is in keeping with findings from a Turkish study (Yesil et al. 2009). Grigoropoulou et al. (2017) in a Greek study have observed that patients with DFU that presented with osteomyelitis tend to stay longer on antibiotics compared with those without osteomyelitis and even with that their outcome is not any better. Osteomyelitis is usually due to non-healing ulcers and it is associated with high risk of major amputation (Giurato et al. 2017). Osteomyelitis in DFU is mostly the consequence of a soft tissue infection that spreads into the bone, involving the cortex first and then the marrow and the most commonly detected bacteria are S. aureus (up to 50% of cases), S. epidermidis (about 25%), Streptococci (about 30%) and Enterobacteriaceae (up to 40%) (Giurato et al. 2017).

We observed that subjects with good glycemic control (HbA1c <7%) were four times more likely to have good wound healing in the univariate analysis, however, this effect was attenuated on multivariate analysis. Reports on the effect of glycemic control on wound healing have been largely conflicting. While some studies observed a significant association between the two (Marston 2006; Monami et al. 2008), others have reported otherwise (Margolis et al. 2000). In our study, multivariate analysis did not show any significant association between glycemic control and wound healing. These findings suggest that although poor glycemia is a potent risk factor for development of DFU, it is not necessarily a significant determinant of wound healing in the patients.

In conclusion, the predictors of wound healing include the presence of osteomyelitis, duration of ulcer greater than 1-month, PAD, Wagner grade 3 or higher, proteinuria, presence of gangrene, anemia, renal impairment and HbA1c ≥7%. Early identification and prompt attention to these factors in a diabetic foot wound might significantly improve healing and reduce adverse outcomes such as amputation and death. More emphasis should be placed on prevention through patient education on care of the foot, while efforts should be made to engage policy makers on the devastation caused by diabetic foot problems and ways of mitigating this challenge.

To our knowledge, the MEDFUN is the largest and the only multi-center study on diabetic foot ulcer not only in Nigeria but also in West-Africa and the only study that extensively investigated the determinants of wound healing in patients with DFU in this subregion. Secondly, our study centers covered 4 out of the six geo-political zones of Nigeria. Since the remaining 2 geo-political zones share common characteristics with one or more of these 4 zones, our results are therefore largely generalizable as a true reflection of the burden of diabetic foot ulcer in Nigeria.

The limitations of this study, however, need to be highlighted. Firstly, distinction between type 1 and type 2 DM was made clinically as commonly practiced in most hospitals in Nigeria due to absence of facilities for routine anti-GAD 65 and plasma C-peptide assays. This may lead to misclassification of subjects by diabetes type. Secondly, our inability to conduct vascular imaging of the lower limbs for all the participants constitutes another limitation. Due to financial difficulties only subjects with clinical suspicion of PAD underwent Doppler ultrasound. This has the potential of under diagnosing the condition due to observer bias. Finally, each of the participating centers adopted its own DFU management protocol based on availability of manpower and the decision to amputate or not was dependent on the clinicians at each center. It is not unlikely that this lack of uniformity might have affected the outcome of this study. This is also applicable to the clinical measurements which are prone to inter-observer bias and laboratory tests which might have been influenced by performance variations of diagnostic equipments at the different study centers.

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