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Can a combination of lifestyle and clinical characteristics explain the presence of foot ulcer in patients with diabetes?

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ABSTRACT

Aims: The aim of this study was to identify the biomechanical, neurological and clinical parameters along with other demographics and lifestyle risk factors that could explain the presence of foot ulcer in patients with diabetes in Africa.
Methods: A total of 1270 (M/F:696/574) patients; 77(M/F:53/24) with ulcerated vs 1193 (M/F: 643/550) with non-ulcerated feet; participated in this study. A set of 28 parameters were collected and compared between the participants with and without active foot ulcers. Multivariate logistic regression was utilised to develop an explanatory model for foot ulceration.
Results: Foot swelling ($\chi2(1,n = 1270) = 265.9, P = 0.000$,Phi = 0.464) and impaired sensation to monofilament ($\chi2(2,n = 1270) = 114.2, P = 0.000$,Cramer'sV = 0.300) showed strong association with presence of ulceration. A lower Temperature sensitivity to cold stimuli and limited ankle joint mobility were observed to be significant ($P < 0.05$) contributors to ulceration. The logistic regression model can justify the presence of foot ulceration with 95.3% diagnostic accuracy, 99.1% specificity and 37.3% sensitivity.
Conclusion: Participants with ulcerated foot show distinct characteristics in few foot related parameters. Swollen foot, limited ankle mobility, and peripheral sensory neuropathy were significant characteristics of patients with diabetic foot ulcer. One out of three patients with ulcerated foot showed common characteristics that could be justified by the model.

1. Introduction

The lifetime incidence rate of Diabetic Foot Ulcers was estimated to be between 15 and 25%[1] and has been recently reported to be between 19 and 34% for persons with diabetes.[2] The rate of ulcer recurrence is approximated to be 65% in 5 years,[2] with more than 50% of diabetic ulcers becoming infected.[3] Approximately 20% of moderate or severe diabetic foot infections lead to some level of amputation[4,5] Diabetic Foot Ulcer (DFU) is the main cause of lower limb amputation in patients with diabetes worldwide.[1] The presence of diabetic foot ulcers in patient increases the risk of death at 5 years by 2.5 times.[6] In order to decrease the socioeconomic cost associated with diabetic foot ulcers, a specific management protocol needs to be developed for patients with ulcerated foot. For developing such protocols, a thorough knowledge of the clinical characteristics of individuals with diabetic foot ulcer is necessary.

There has been an abundance of studies on the predictive factors for diabetic foot ulceration.[7] A recent systematic review of literature and meta-analysis reported that insensitivity to a 10-g monofilament or one absent pedal pulse as established prognostic factors that identify patients with moderate or intermediate risk of foot ulceration.[8] While history of DFUs or lower-extremity amputations were reported to be sufficient to identify those at high risk of developing DFU,[8] the studies of patients with active DFU in large cohort (>200 participants) have been much less frequent.[9–13]

A previous study of patients with active DFU in Australian population have identified that the duration of diabetes, neuropathy and vascular insufficiencies are associated with DFU;[9] while in a study on Asian population age and cigarette smoking were identified as characteristics of patients with DFU.[10] Another study in North Europe found that age, male gender and macrovascular complications were associated factors for participants with a previous or current DFU. People with DFU were reported to be significantly taller than those who never had DFU.[11] In a study conducted on South American population male gender, smoking, neuroischmeic foot and absence of vibration perception

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were found to be associated with participants with previously healed or current DFU.[12] In another study on North American population loss of protective sensation, history of amputation, elevated plantar pressure, foot deformities, poor diabetes control, duration of diabetes and male sex were found to be associated with participants with current or recently healed DFU.[13] Despite these, there is a scarcity of studies in which characteristics of patients with current DFU is considered in a large cohort in Africa.

While poor glycaemic control was commonly reported as a risk factors for diabetic foot ulceration,[14] in a study involving smaller cohort of patients alcohol consumption was found to be significantly higher in patients with active DFU compared to those with no DFU.[15]

Impaired thermal sensation, associated with small fibre neuropathy has also been associated with presence of neuropathic DFU in small patient population.[16] Despite this, the differences in thermal sensation between ulcerated and non-ulcerated and the association between thermal sensitivity and DFU have not been previously investigated in a large cohort of patients. In addition, although recent studies on smaller groups of patients have shown that the plantar pressure is significantly higher in patients with DFU, compared to their non-ulcerated counterparts,[17] with the exception of few studies i.e.[13] this has not been confirmed in other large cohort of patients.

The aim of this study was to identify the biomechanical, neurological and clinical parameters along with other demographics and lifestyle risk factors that could explain the presence of DFU in patients with diabetes from African population.

The first objective of this study is to identify the differences in biomechanical, neurological, clinical, demographics and lifestyle parameters between patients with DFU against other patients without DFU. The second objective of this study was to propose an explanatory model that can justify the presence of DFU in this group of patients based on their common characteristics.

2. Material and method

2.1. Participants

Patients who attended the diabetic foot clinic in Tanzania between Jan 2011 and Dec 2015 were recruited to participate in this study. Ethical approval was sought and granted by the local ethics committee and informed consent was obtained from all participants. DFU was defined as a full-thickness wound involving the foot or the ankle, distal to and including the malleoli. The sample size was calculated as 1128 participants based on the prevalence of foot ulceration rate of 10%, in the studied group and DFU prevalence of 7% in diabetes population in Africa[18] with Alpha level of 5% and power of 95%. Assuming a missing data in 1 out 8 participants, an additional 142 participants were needed to be recruited to the study to ensure that the calculated sample size is used in every statistical analysis.

2.2. Data collection

A combination of categorical and continuous parameters (as follows) were collected from the patients during a single visit.

2.2.1. Categorical parameters

The general categorical parameters were: Smoking (Current smoker, Never smoked, Previous smoker), Alcohol habits (Currently drinks, Never drunk, in the past), Previous amputation, and History of Ulceration according to protocols set by IWGDF.[19]

The foot-specific categorical parameters included: Neuropathy (using 10-g monofilament loss of sensation)[20] was assessed on both feet at 10 sites including Hallux, 3rd Toe, 5th Toe, 1st Met head, 3rd Met head, 5th Met head, lateral midfoot, medial midfoot, centre of the hindfoot, and dorsum of the foot.[21] For sensitivity to monofilament each patient was categorised into 3 levels as having Normal (sensation present in >8 sites), Decreased (sensation present in 4–7 sites) and Absent (sensation is felt in <3 sites).

Foot deformity was assessed as structural abnormalities in the foot such as Claw/Hammer Toe and Hallux Valgus or prominent metatarsal heads, status after Charcot foot, amputations and other foot surgery were considered as having foot deformity.[22]

Skin status was considered as: Dry when Epidermis that lacks moisture or sebum; Fissures: characterized by a pattern of fine lines, scaling, and fissures; and Normal: well-balanced skin eudermic that is neither too oily nor too dry.[23,24] Mycosis was considered as fungal infection in between the toes and macerated skin.[23]

Nail ingrowth was considered as in-growing toe nail (also known as onychocryptosis) and it was considered as present when the nail grows so that it cuts into one or both sides of the paronychium or nail bed.[23] Swelling was considered as present when swelling of foot sufficiently pronounced to leave a clear imprint of the pressure by a finger.[23] Presence of callus was also considered to be present based on the protocol proposed in IWGDF guidelines.[23]

Specific categorical parameters for each participant were defined as if these occurred on either or both feet.

2.2.2. Continuous parameters

The general continuous parameters included: Age, Body mass, Height, Shoe size (UK), Duration of Diabetes, and Body Mass Index. The foot-specific continuous parameters were: Ankle Brachial Pressure Index (ABPI), Vibration Perception Threshold, Temperature Sensation and Tolerance Thresholds and plantar pressure.

Vibration Perception Threshold was measured using a clinically accepted device (Neuropathy Analyser – Vibrotherm – Dx -Diabetik Foot Care India Pvt. Ltd., Chennai, India) at the wrist, knee, ankle and big toe according to the previous protocol.[25] This device was also used to measure the Temperature Sensation and Temperature Tolerance Thresholds to cold/warm at: Hallux, 3rd Toe, 5th Toe, underneath the arch and Heel according to the previous protocol.[26]

A plantar pressure platform (EMED, Novel, Munich, Germany) was utilised to measure average plantar pressure during the stance phase of walking at 16 sites (Hallux, 2nd Toe, 3rd Toe, 4th Toe, 5th Toe, 1st Met head, 2nd Met head, 3rd Met head, 4th Met head, 5th Met head, lateral midfoot, central midfoot, medial midfoot, lateral hindfoot, medical hindfoot, centre of the hindfoot), based on previous protocol[27]. This allowed the toes, heel and midfoot regions to be divided into more specific regions for further in-depth analyses of the plantar pressure. The participants were asked to walk over the platform using a two-step protocol[28] after completing a number of familiarisation trials. The mean of average pressures from 3 stance phases from each foot were calculated based on which the overall and regional pressures were reported.[29] All specific continuous parameters were averaged between the left and right feet.

2.3. Data analyses

All statistical tests were performed using IBM® SPSS®v.25.

2.3.1. Test of differences

Chi-square test for independence with Yates Continuity Correction was utilised to identify significant ($P < 0.05$) association between categorical parameters and the prevalence of DFU.

Furthermore, given the non-normal distribution of the data which was established through the test of normality (Kolmogorov-Smirnov, $P < 0.05$), Mann-Whitney U Test was utilised to assess significant ($P < 0.05$) differences in continuous parameters between the patients with and without ulceration.

2.3.2. Explanatory model for foot ulceration

Multivariate logistic regression was utilised to develop the explanatory model for foot ulceration based on the risk factors. Logistic

Table 1
Blocks representing each set of covariates that were added to reach the final explanatory model.

Block	Parameters
1	Age, Sex, Weight, Height, Body Mass Index (BMI), Shoe size, Diabetes duration, Smoking habit, Alcohol consumption, and Fasting Blood Sugar Level
2	History of amputation, Previous ulceration, presence of Callus, Foot deformity, Swelling, and Nail ingrowth
3	Ankle Brachial Index, MTP joint mobility and Ankle joint mobility
4	Vibration Perception Threshold, and sensitivity to Monofilament
5	Vibration Perception Thresholds at Wrist, Knee, Ankle and Hallux
6	Temperature Sensation and Tolerance Thresholds to Cold probe at Hallux, 1st Toe, 3rd Toe, 5th Toe, underneath the arch, Heel and the average and the total corresponding values for these sites
7	Temperature Sensation and Tolerance Thresholds to Hot probe at Hallux, 1st Toe, 3rd Toe, 5th Toe, underneath the arch, Heel and the average and the total corresponding values for these sites
8	Plantar Pressure at the lateral midfoot, central midfoot, medial midfoot, lateral hindfoot, medical hindfoot, and centre of the hindfoot
9	Plantar Pressure at the Hallux, 2nd Toe, 3rd Toe, 4th Toe, 5th Toe, 1st Met head, 2nd Met head, 3rd Met head, 4th Met head, and 5th Met head

regression was used to justify the presence or absence of ulceration based on values of a set of predictor variables (covariates).

To identify the effect of each set of parameters on the accuracy of the explanatory model, the covariates were entered through 9 blocks of parameters as shown in Table 1.

These blocks were decided based on a hierarchical fashion in which clinically plausible set of similar parameters were included in each consecutive block that were sorted based on increase in the complexity level. Furthermore, for a set of parameters across different blocks, diagnostic test of multicollinearity (with tolerance value of 0.1 or $R^2 > 0.9$) was performed and ensured no independent parameters (covariate) existed across blocks.

In each block of parameters, an automated backward stepwise selection algorithm (retaining variables with $P < 0.05$ removal testing is based on the probability of the Wald statistic) was used to arrive at the multiple regression model. The collinearity between independent parameters in the same block was taken care of by the automated backward stepwise selection algorithm.

Logistic regression coefficients were also used to estimate odds ratios for each of the independent variables along with the significance of the parameters in the model. Chi-square and significance level based on Hosmer-Lemeshow goodness of fit was used to indicate how worthwhile the model was in explaining the presence of ulceration. Furthermore Cox & Snell and Nagelkerke R-Square values provided an indication of a pseudo R square value that indicates the upper and lower range of variability in ulceration status that can be explained by the model.

The sensitivity (as the percentage of participants with DFU incidence that are identified as having DFU) and specificity (as the percentage of participants with no ulceration incidence that are identified as not having DFU) along with the overall explanatory accuracy (as the percentage of the entire cases that are explained correctly) of the method were

Table 2
Shows the categorical parameters for all participants and for the each group with and with no ulceration.

Categorical variable	All (1270)		No ulceration (1193–93.9%)		With ulceration (77–6.1%)						
	No	%	No	%	No	%	Odd ratio (CI at 95%)	*P* value multi-variate analyses	*P* value for differences[a]	Effect size for difference	Effect size classification
Male sex	696	54.8	643	53.9	53	68.8	1.488 (0.784–2.825)	0.224	0.010	−0.072[b]	Small
Previous ulceration	13	1.0%	10	0.8%	3	3.9%			0.046	0.072[b]	Small
Amputation	4	0.3%	0	0.0%	4	5.2%	2.932 *10^9 (0- ∞)	0.999	0.000	0.221[b]	Med
Presence of callus	209	16.5%	199	16.7%	10	13.0%			0.491	−0.024[b]	
Foot deformity	26	2.0%	19	1.6%	7	9.1%	3.816 (0.826–17.632)	0.086	0.000	0.126[b]	Small/med
Mycosis	34	2.7%	31	2.6%	3	3.9%			0.794	0.019[b]	
Nail ingrowth	4	0.3%	2	0.2%	2	2.6%			0.008	0.103[b]	Small
Foot swelling	76	6.0%	38	3.2%	38	49.4%	16.456 (8.199–33.028)	0.000	0.000	0.464[b]	Large
No smoking (Ref)	984	77.5%	930	78.0%	54	70.1%					
Past smoker	216	17.0%	199	16.7%	17	22.1%			0.298	0.045[c]	
Current smoker	70	5.5%	64	5.4%	6	7.8%					
No alcohol cons. (Ref)	721	56.8%	681	57.1%	40	51.9%					
Past alcohol cons.	392	30.9%	362	30.3%	30	39.0%			0.255	0.047[c]	
Current alcohol cons.	157	12.4%	150	12.6%	7	9.1%					
Ankle joint normal mobility	1051	82.8%	1013	84.9%	38	49.4%	0.438 (0.231–0.834)	0.012	0.000	−0.225[b]	Med
MTP joint normal mobility	1049	82.6%	1011	84.7%	38	49.4%			0.000	−0.223[b]	Med
Skin viability normal (Ref)	125	9.8%	124	10.4%	1	1.3%					
Skin viability dry	1127	88.7%	1054	88.3%	73	94.8%			0.002	0.089[c]	Small
Skin viability dry with fissures	18	1.4%	15	1.3%	3	3.9%					
Sensitivity to monofilament -absent (Ref)	45	3.5%	28	2.3%	17	22.1%		0.177			
Sensitivity to monofilament-impaired	329	25.9%	292	24.5%	37	48.1%	0.652 (0.229–1.861)	0.424	0.000	0.300[c]	Large
Sensitivity to monofilament -normal	896	70.6%	873	73.2%	23	29.9%	0.337 (0.096–1.180)	0.089			

[a] - *P* values based on Chi-square test of independence (with Yates continuity correction) $P < 0.5$ indicates significant association between ulcerated and non-ulcerated group on the parameter.
[b] - Effect size as the Phi coefficient, with Small = 0.01, Medium = 0.30, Large = 0.50.
[c] - Effect size as Cramer's V coefficient (three categories), where Small = 0.07, Medium = 0.21, Large = 0.35.

Table 3
Shows the continuous parameters for all participants and for the groups with and with no ulceration.

Continuous parameter	All			No-ulceration			With ulceration			OR (CI at 95%)	P-Multi-variate	P-Differences	Effect size[a] difference	Effect size category
	Median	IQR	N	Median	IQR	N	Median	IQR	N					
Age (year)	52	17.0	1270	52	12.5	1193	53	17.0	77			0.177	−0.038	
Height (m)	1.60	0.1	1270	1.60	0.1	1193	1.60	0.1	77			0.020	−0.065	Small
Weight (kg)	73.7	20.7	1268	73.6	18.1	1191	74.0	20.8	77			0.752	−0.009	
Body Mass Index (kg/m^2)	29.4	7.5	1270	29.4	5.5	1193	29.1	7.9	77			0.143	−0.041	
Shoe size	8	2.0	1268	7	2.0	1191	8	2.0	77			0.117	−0.044	
Ankle Brachial Index (ABI)	1.1	0.1	1270	1.1	0.1	1193	1.1	0.1	77			0.864	−0.005	
Vibration perception threshold average (V)	20	14.3	1270	20	15.5	1193	35	15.0	77			0.000	−0.221	Med
Vibration perception threshold wrist (V)	11	4.0	1270	11	3.5	1193	14	3.5	77			0.000	−0.178	Med
Vibration perception threshold knee (V)	22	12.0	1267	22	10.0	1190	30	11.5	77			0.000	−0.193	Med
Vibration perception threshold ankle (V)	21	13.5	1270	20	13.3	1193	34	13.0	77			0.000	−0.222	Med
Vibration perception threshold hallux (V)	21	15.0	1270	21	16.5	1193	36	15.0	77			0.000	−0.231	Med
Duration of diabetes (days)	1095	2747.5	1270	1095	4380.0	1193	2920	2770.0	77	1.017 (0.973–1.064)	0.453	0.000	−0.167	Med
Plantar pressure at Hallux (kPa)	253	155.0	1270	255	171.3	1193	215	152.9	77			0.007	−0.075	Small
Plantar pressure at 2nd Toe (kPa)	133	88.0	1270	135	78.8	1193	115	87.5	77			0.006	−0.078	Small
Plantar pressure at 3rd toe (kPa)	88	67.5	1270	90	57.5	1193	68	65.0	77			0.000	−0.102	Small
Plantar pressure at 4th toe (kPa)	58	50.0	1270	60	30.0	1193	48	52.5	77			0.002	−0.086	Small
Plantar pressure at 5th toe (kPa)	30	37.5	1270	30	25.0	1193	18	37.5	77	0.977 (0.862–0.992)	0.003	0.000	−0.105	Small
Plantar pressure 1st MTH (kPa)	160	80.0	1270	158	83.8	1193	193	79.0	77			0.004	−0.081	Small
Plantar pressure at 2nd MTH (kPa)	205	90.0	1270	205	86.3	1193	215	90.0	77			0.239	−0.033	
Plantar pressure at 3rd MTH (kPa)	228	90.0	1270	228	86.3	1193	223	90.0	77			0.421	−0.023	
Plantar pressure at 4th MTH (kPa)	213	82.5	1270	213	97.5	1193	220	82.5	77			0.214	−0.035	
Plantar pressure at 5th MTH (kPa)	180	95.0	1270	180	121.3	1193	198	95.0	77			0.042	−0.057	Small
Plantar pressure at lateral midfoot (kPa)	78	40.0	1270	78	37.5	1193	78	40.0	77			0.630	−0.014	
Plantar pressure at central midfoot (kPa)	101	57.5	1270	101	65.0	1193	98	57.5	77			0.604	−0.015	
Plantar pressure at medial midfoot (kPa)	68	35.0	1270	68	31.3	1193	68	35.0	77			0.670	−0.012	
Plantar pressure at lateral hindfoot (kPa)	115	50.0	1270	115	56.8	1193	110	50.0	77			0.604	−0.015	
Plantar pressure at medical hindfoot (kPa)	170	52.5	1270	170	50.0	1193	173	52.5	77			0.915	−0.003	
Plantar pressure at central hindfoot (kPa)	122	62.5	1270	123	68.8	1193	118	62.5	77	1.004 (0.998–1.010)	0.178	0.595	−0.015	
TST to cold probe at Hallux (°C)	29	3.0	1254	29	0.5	1178	27	3.0	76			0.000	−0.207	Med
TST to hot probe at Hallux (°C)	38	6.0	1253	38	1.0	1177	40	6.0	76			0.000	−0.197	Med
TTT to cold probe at Hallux (°C)	21	3.0	1254	21	0.8	1178	19	3.0	76			0.000	−0.188	Med
TTT to hot probe at Hallux (°C)	45	3.5	1254	45	1.3	1178	47	3.5	76			0.000	−0.219	Med
TST to cold probe at 3rd toe (°C)	29	2.5	1254	29	0.5	1178	27	2.5	76			0.000	−0.205	Med
TST to hot probe at 3rd toe (°C)	37	5.0	1254	37	0.5	1178	40	5.0	76			0.000	−0.191	Med
TTT to cold probe at 3rd toe (°C)	21	2.5	1253	21	1.0	1177	19	2.5	76			0.000	−0.173	Med
TTT to hot probe at 3rd toe (°C)	45	3.5	1254	44	1.5	1178	47	3.5	76			0.000	−0.198	Med
TST to cold probe at 5th toe (°C)	29	2.0	1253	29	1.0	1177	27	2.0	76			0.000	−0.196	Med
TST to hot probe at 5th toe (°C)	38	5.0	1254	38	1.0	1178	40	5.5	76			0.000	−0.192	Med
TTT to cold probe at 5th toe (°C)	21	3.0	1254	21	1.5	1178	19	3.0	76			0.000	−0.191	Med
TTT to hot probe at 5th toe (°C)	44	3.5	1254	44	1.3	1178	47	3.5	76			0.000	−0.219	Med
TST to cold probe underneath the arch (°C)	28	3.0	1254	29	0.5	1178	27	3.0	76			0.000	−0.192	Med
TST to hot probe underneath the arch (°C)	38	4.0	1254	38	0.5	1178	40	4.0	76			0.000	−0.189	Med
TTT to cold probe underneath the arch (°C)	20	3.0	1254	21	1.3	1178	19	3.0	76			0.000	−0.174	Med
TTT to hot probe underneath the arch (°C)	45	3.0	1254	45	1.0	1178	47	3.0	76	1.423 (0.999–2.028)	0.051	0.000	−0.215	Med
TST to cold probe at heel (°C)	29	3.0	1254	29	0.3	1178	27	3.0	76			0.000	−0.179	Med
TST to hot probe at heel (°C)	38	3.0	1254	38	1.0	1178	40	3.0	76			0.000	−0.168	Med
TTT to cold probe at heel (°C)	21	3.0	1254	21	2.0	1178	19	3.0	76			0.000	−0.159	Med
TTT to hot probe at heel (°C)	45	3.0	1254	45	1.5	1178	48	3.0	76			0.000	−0.203	Med
TST to cold probe total (°C)	144	12.5	1254	144	4.3	1178	133	12.0	76	0.998 (0.927–1.074)	0.955	0.000	−0.236	Med
TST to hot probe total (°C)	185	23.5	1254	185	16.5	1178	198	24.0	76			0.027	−0.062	Small
TTT to cold probe total (°C)	104	13.5	1254	104	7.5	1178	93	13.5	76			0.000	−0.174	Med
TTT to hot probe total (°C)	221	17.0	1254	220	19.5	1178	233	16.5	76	0.975 (0.948–1.003)	0.080	0.170	−0.039	
TST to cold probe average (°C)	29	2.5	1248	29	0.4	1173	27	2.4	75	0.630 (0.445–0.891)	0.009	0.000	−0.218	Med
TST to hot probe average (°C)	37	4.7	1254	37	1.0	1178	40	4.9	76			0.000	−0.154	Med
TTT to cold probe average (°C)	21	2.7	1251	21	0.9	1175	19	2.7	76	1.399 (1.096–1.786)	0.007	0.000	−0.167	Med
TTT to hot probe average (°C)	44	3.3	1251	44	0.8	1175	47	3.3	76			0.000	−0.195	Med
Blood glucose level (mmol/L)	12	7.9	1269	12	7.0	1192	10	7.9	77	0.938 (0.885–0.995)	0.032	0.002	−0.085	Small

[a] - Mann-Whitney; $r = z/(N_1 + N_2)^{0.5}$ where 0.1 small effect, 0.3 medium effect, 0.5 large effect. Note that the selection of parameters in the logistic regression model was based on the univariate analyses in which parameters with $P < 0.2$ were selected. The P values for these selected parameters are underlined in the table.

reported when the consecutive blocks[1–9] were added. Furthermore, using the area under the receiver operating characteristic (ROC) curve with 95% confidence levels were calculated and referred to as the diagnosis strength of the model.

3. Results

A total of 1270 (M/F: 696/574) participants as 77 (M/F: 53/24) with ulcerated vs 1193 (M/F: 643/550) with non-ulcerated feet were recruited to the study. Tables 2, and 3 represent the results related to the test of differences along with the bivariate and multivariate logistic regression for the categorical and continuous parameters respectively. While there was no missing data for the categorical and for the majority of continuous parameters, the TST and TTT data were missing for 16–19 participants, and the VPT at knee and Blood Glucose level data were missing for 1 and 3 participants respectively. The missing data was accounted for in all statistical analyses, as indicated in Tables 2 and 3.

3.1. Differences in categorical parameters

In comparing the general categorical parameters between the two groups, it was found that male gender, was significantly ($P = 0.010$) associated with presence of ulceration with a small effect size. Significant associations for foot swelling ($P = 0.000$) and impaired sensation to monofilament ($P = 0.000$) were observed with presence of ulceration (both with large effect size). Also, amputation, foot deformity ($P = 0.000$), Ankle joint limited mobility ($P = 0.000$) and MTP joint limited mobility ($P = 0.000$) were all significantly associated with ulcerated group (medium effect size). It should also be mentioned that previous ulceration ($P = 0.046$), nail ingrowth ($P = 0.008$) and skin dryness level ($P = 0.002$) were all associated significantly with ulcerated group (small effect size).

3.2. Differences in continuous parameters

While comparing general continuous parameters between the two groups, the results of this study indicate that the ulcerated group were significantly ($P = 0.020$) taller (small effect size) and had significantly ($P = 0.000$) longer duration of diabetes (medium effect size).

Furthermore, in comparison of foot specific continuous parameters between the two groups, the ulcerated group showed a significantly ($P = 0.000$) average higher vibration perception threshold (Medium effect size).

While the plantar pressure were significantly lower at Hallux ($P = 0.007$); 2nd toe ($P = 0.006$); 3rd toe ($P = 0.000$); 4th Toes ($P = 0.002$); and 5th Toe ($P = 0.000$) in ulcerated patients the plantar pressure at the 1st ($P = 0.004$) and 5th MTH ($P = 0.042$) showed to be significantly higher in ulcerated patients compared to non-ulcerated patients (all with small effect size).

The average, total, and all site-specific TTT and TST to cold probe was significantly ($P = 0.000$) lower for the ulcerated group, while the corresponding values for TTT and TST to hot probe were significantly ($P = 0.000$) higher in ulcerated group (all with Medium effect size).

The VPT at wrist, knee, ankle and Hallux was significantly ($P = 0.000$) higher in ulcerated group (all with medium effect size), while Blood Glucose level showed to be significantly ($P = 0.002$) lower in ulcerated patients (small effect size).

3.3. Explanatory model for DFU

Hosmer-Lemeshow goodness of fit indicated that the model was worthwhile indicated by the goodness of fit test results ($\chi^2 = 4.882$, $P = 0.770$) that indicated that the hypothesis of a good fit is not rejected ($P > 0.05$).

The result of multiple regression analyses with backward stepwise selection algorithm (retaining variables with $P < 0.05$) indicated that only 15 (6 categorical and 9 continuous) parameters stayed in the final model. From categorical parameters, only the presence of foot swelling (OR = 16.456; 95%CI = 8.199–33.028; $P = 0.000$) and normal ankle mobility (OR = 0.438; 95%CI = 0.231–0.834; $P = 0.012$) contributed significantly to justification of presence of DFU (Table 2 and Fig. 1).

From continuous parameters only four parameters including lower blood sugar level (OR = 0.938; 95%CI = 0.885–0.995; $P = 0.032$), lower average TST to cold (OR = 0.630; 95%CI = 0.445–0.891; $P = 0.009$), higher Average TTT to cold (OR = 1.399; 95%CI = 1.096–1.786; $P = 0.007$), and lower plantar pressure at the fifth toe (OR = 0.977; 95%CI = 0.862–0.992; $P = 0.003$) were shown to be significant identifiers of ulcerated patients.

Fig. 1 shows the effect of each set of parameters on the explanatory accuracy of the model, where the covariates were entered through 9 blocks.

As indicated in Fig. 1, while the sensitivity shows a significant increase from Block 1 (0%) to Block 9 (37.3%), the specificity of the model dropped only marginally by 0.8% from Block 1 (99.9%) to Block 9 (99.1%). This has led to the identification accuracy of the model to improve only marginally by 1.5% (from 93.8% to 95.3%). It was observed that the diagnosis strength of the model was also increased from 70.5% in Block 1 to 73.7% in Block 9.

The model as a whole could justify between 17.4% (Cox and Snell R Square) and 47.1% (Nagelkerke R Square) of the variation in ulceration status.

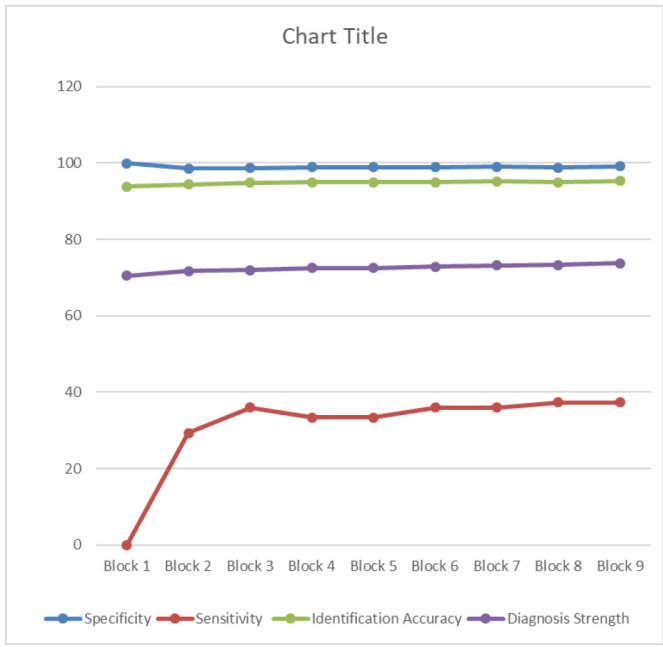

Fig. 1. The Sensitivity (percentage of the group with ulceration occurrence that is correctly identified by the model), Specificity (percentage of the group with No ulceration occurrence that is correctly identified by the model), Identification Accuracy (percentage of the overall group that is correctly identified by the model), along with the Diagnosis Strength (the areas below the Receiver Operation Curve) of the model when the covariates are added in sequential order from left to right. Block 1: The model includes covariate A, B & C; Block 2: The model includes covariates: A, B, C, D, E & F; Block 3: The model includes covariates: A, B, C, D, E, F & G; Block 4: The model includes covariates: A, B, C, D, E, F, G & H; Block 5: The model includes covariates: A, B, C, D, E, F, G H I & J ; Block 6: The model includes covariates: A, B, C, D, E, F, G, H, I, J & K; Block 7: The model includes covariates: A, B, C, D, E, F, G, H, I, J, K, & L and M; Block 8: The model includes covariates: A, B, C, D, E, F, G, H, I, J, K, L, M & N; Block 9: The model includes covariates: A, B, C, D, E, F, G, H, I, J, K, L, M, N & O. Where A: Sex (Male:1, Female:2); B: Duration of Diabetes (in days); C: Blood Glucose level (mmol/L); D: Amputation (0: without, 1:with); E: Foot deformity (0 without, 1 with); F: Foot swelling (0:without, 1: with); G: Ankle Mobility (0:without, 1:with); H: Sensitivity to monofilament (0: Absent, Decreased: 1, Normal: 2); I: Sum of Temperature Sensitivity Threshold to cold probe (°c); J: Average Temperature Sensitivity Threshold to cold probe(°c); K: Average Temperature Tolerance Threshold to cold probe(°c); L: Temperature Tolerance Threshold to hot probe underneath the arch(°c); M: Sum of Temperature Tolerance Threshold to hot probe (°c); N: Plantar pressure at the centre of the Heel (kPa); O: Plantar pressure at the Fifth Toe (kPa).

4. Discussion

4.1. Difference in categorical parameters

When, comparing the general categorical parameters between the two groups, it was found that male gender, was associated with presence of DFU with a small effect size. This has been in line with the previous studies in which significantly higher proportion of patients with DFU reported to be male in western population in the North America,[13] and in North Europe.[11] However these findings are contrary to the study in Australian population where no significant difference in the proportion of male sex in the ulcerated vs non-ulcerated population was reported.[9]

In this study previous amputation was found to be significantly higher in the ulcerated group which is in line with the results of previous studies on North European[11] population.

From the specific categorical parameter, impaired sensation to monofilament showed significant association with presence of ulceration with a large effect size (Cramer's V coefficient = 0.3), indicates the relationship between sensory neuropathy and DFU and is in line with previous studies on Australian[9] population.

The results of the current study in which a significantly higher number of participants with swollen feet was observed in the ulcerated (vs non-ulcerated) group with a large effect size (Phi coefficient = 0.464) was never reported in previous studies. While the difference cannot indicate a causal relationship between ulcer and presence of foot swelling, the finding can have implications in designing footwear interventions for this group of patients.

Foot deformity has been associated with a medium effect size in the current study. Although there is no study with comparable population size against which the results of this study can be compared, our findings are in line with the results by Fernando and co-workers[17] who reported significantly higher proportion of patients with Hammer toe deformity in the ulcerated group compared to the group with diabetic neuropathy.

The inconclusive results of this study regarding the contribution of Alcohol ingestion to justifying the risk of diabetic foot ulceration are in line with previous findings on Australian,[9] North American[13] and Asian[10] population. Furthermore the inconclusive results of the current study regarding smoking as a contributing factor to justify the presence of DFU are in line with the previous study in North European,[11] North American[13] and Australian[9] population, while it contradicted the results on South American[12] and Asian[10] populations where smoking was reported as a contributing factor to justify diabetic foot ulceration.

Ankle and MTP joint limited mobilities were all associated with ulcerated group (medium effect size), that is in contrary to the findings by Fernando and co-workers[17] in which no significant difference was found between either of the parameters and ulceration.

4.2. Difference in continuous parameters

The results of this study are in line with the previous literature in which patients with ulcers have shown to have higher duration of diabetes compared to their non-ulcerated counterparts i.e. in studies of South American,[12] North European[11] and Australian[9] populations.

While the results of the current study indicated that the ulcerated group were significantly taller that is in line with findings on North European population,[11] the results of the current study are contrary to the findings reported for Australian population,[9] which found no significant difference in height of ulcerated and non-ulcerated group.

The results of the current study on the plantar pressure at the toes also contradict the results by Fernando and co-workers [17] who reported a significantly higher pressure at these sites in patients with DFU. Although the difference may be due to the fact that the previous study [17] measured pressure at the entire area under the lesser toes, the current study measured the pressure under toes separately.

Furthermore, the results of the current study indicate that the plantar pressure at the 1st and 5th MTH are significantly higher in ulcerated patients when compared to non-ulcerated patients (all with small effect size). However no such significant differences were reported by Fernando and co-workers.[17]

Also as opposed to the previous study,[17] the current study found no significant difference in the plantar pressure at the midfoot between the ulcerated and non-ulcerated group. This may also be related to the fact that in the current study 3 different zones of midfoot were considered separately.

The average, total, and all site-specific TTT and TST to cold probe were significantly lower for the ulcerated group, while the corresponding values for TTT and TST to hot probe at all tested sites were significantly higher in ulcerated group (all with Medium effect size). This distinct feature of ulcerated patients indicates a pronounced presence of small fibre neuropathy that is in line with the previous findings.[16]

The values of average VPT at foot and VPT at wrist, knee, ankle and Hallux that were significantly higher in ulcerated group (medium effect size) are in line with our earlier findings that indicated that a significantly higher number of participants with ulcerated foot showed neuropathy.

While the finding of this study indicated that the Blood Glucose level showed to be significantly lower in ulcerated patients (small effect size) seems to be contradictory to previous studies in North Europe[11], Australia[9] and South America[12] where Glycated Haemoglobin (HbA1c) was reported to be significantly higher in ulcerated vs non-ulcerated group. However the reduced blood sugar level in ulcerated group in the current study may be the effect of trauma rather than being an existing condition before the ulceration.

4.3. The explanatory model

The model was adequately specific in identifying the factors that protect the patients against ulceration. However, the ability of model in justifying the characteristics of patients with ulcerated foot is currently relatively limited. Approximately 1 out of three patients with ulcerated foot demonstrated common characteristics based on the parameters that were investigated in this study. However comparison between this model that is proposed in the current study against what was proposed for other patient populations in North America,[13] South America,[12] North Europe[11], Asia[10] and Australia[9] is not possible as those (9-13) have not reported the accuracy of the model in terms of sensitivity, specificity and diagnosis power.

Only six parameters (foot swelling, ankle joint mobility, blood Glucose Level, Average TTT and TST to cold probe and plantar pressure at the fifth toe) were found to be significantly ($P < 0.05$) contributed to the model in the current study.

In essence the findings indicate that a patient with swollen foot is approximately 16 times (OR = 16.456) more likely to have DFU and that patients with normal ankle mobility are less than half likely (OR = 0.438) to have DFU.

It is interesting to observe that none of the parameters that were found in the explanatory model of the current study are among parameters that were reported to be significant risk factors for diabetic foot ulceration in previous studies on different patient populations in North America,[13] South America,[12] North Europe[11], Asia[10] and Australia.[9]

It is also worth mentioning that with the exception of Blood Glucose Level all other parameters that significantly contributed to justify the presence of DFU in this study were foot specific.

Furthermore, in the current study plantar pressure at the fifth toe was the only plantar pressure parameter that was found to be a significant contributor to the explanatory model of ulceration. In the current study an increase in the plantar pressure at the fifth toe has been affiliated to decreased risk of foot ulceration with the Odd Ratio of 0.977. This is contrary to the previous study where excessive plantar pressure (>650 kPa) had been found to be significantly (OR = 5.9, $P < 0.001$)

contributing to the explanatory model for foot ulcer.[13] This can be related to the fact that an increase in the plantar pressure at the fifth toe could decrease the pressure at other plantar sites of the foot by offloading the critical areas of the foot.

Although from the demographic parameters male sex (OR = 1.44) was also included in the final model contrary to previous studies in South American (OR = 1.71)[12] and North American (OR = 2.7)[13] population, the contribution of sex to diagnosis power of the model was not significant ($P > 0.05$).

Similarly in line with the previous study on North American population,[13] previous amputation was included in the final ulceration risk diagnostic model, however the contribution was not significant ($P > 0.05$).

Overall the differences in the results of the diagnostic model in this study compared to what we reported previously [9–13], could be the result of the differences in the selected parameters and the participants population.

4.4. Strength and limitations

This study is unique in a sense that it reports a wide range of foot-specific parameters in a big cohort of Diabetic patients in Africa. In addition, this is the first study to report on a wide range of foot-related characteristics along with the clinical and lifestyle factors in patients with DFU compared against those without. The results of this study can have an impact on future research as it provided further evidence of the importance of including foot-specific parameter in the DFU risk diagnostic models. It should be mentioned that the results of the current study indicate that the model could justify the lack of DFU with specificity of 99.1%. Despite the inclusion of number of foot-specific parameters in this study, the final model can only justify the presence of foot ulcer with 37.3% sensitivity.

4.5. Clinical implications and future directions

The results of this study can indicate a trend toward considering more foot-specific parameters in identifying the risk of diabetic foot ulceration in patients. Additionally, the results can be used to develop specific intervention for diabetic patients with active DFU that is suitable to the distinct characteristics of these patients against their non-ulcerated counterparts. These characteristics include the presence of swelling, limited ankle range of motion and distinct small fibre neuropathy.

It is worth mentioning that the group of parameters related to the temperature tolerance and sensitivity thresholds to hot and cold stimuli have shown to be significantly contributors to explaining foot ulceration.

Although a vast range of parameters were collected from each participant , in future the inclusion of further parameters to reflect the micro circulatory,[30] and mechanical properties of the plantar soft tissue[31] could result in a more comprehensive model of diabetic foot ulceration risk.

While few studies have reported severe abnormalities in the temperature tolerance and sensitivity thresholds in ulcerated foot[16,32], these parameters have not been previously investigated in large cohort studies of this nature. The results of the current study justify the need to assess small fibre neuropathy as a risk factor for foot ulceration in diabetic patients. As outlined in a recent critical evaluation of the diabetic foot screening guidelines there is a clear need for more structured data that can provide evidence for the development of screening guidelines.[33]

5. Conclusion

Overall, the participants with ulcerated foot show distinct characteristics in a number of clinical parameters including pronounced impaired sensation and foot swelling.

The combination of parameters collected in this study can explain the common characteristics of patients that can be protective against foot ulceration. However only 1 out of three patients with ulcerated foot show common characteristics that can be considered as risk factors for ulceration.

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