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CLINICAL INVESTIGATION OF DISEASE COMPLICATION LEVEL IN ADULT DIABETIC FOOT ULCER PATIENTS: PERIPHERAL NEUROPATHY, PERIPHERAL VASCULAR DISEASE, AND GLYCAEMIC CONTROL

A CROSS-SECTIONAL STUDY AT GAMBAT INSTITUTE OF MEDICAL SCIENCES, KHAIRPUR, SINDH, PAKISTAN

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Abstract

Peripheral diabetic neuropathy (PDN), peripheral vascular disease (PVD) and prolonged fluctuations in blood glucose level comprise the deadly triad of factors that transforms poorly managed diabetes mellitus type 2 (DM2) into limb-threatening diabetic foot ulcer (DFU). The measurement of the severity of these risk factors in DFU patients through well-defined tests is crucial to gauge disease complication level and plan treatment.

This study aimed to explore the clinical complication level of Diabetes Foot Ulcers (DFU) patients using four standardised tests Body Mass Index (BMI), Ankle Brachial Index (ABI) for PVD, 10g Monofilament Test (10g MFT) for PDN and HbA1c for chronic hyperglycaemia; to describe Wagner ulcer grades and linear regression between HbA1c and ABI.

Methods: *100 adult DFU patients (non-selective consecutive cross-sectional study) were investigated at OPD, GIMS in Khairpur, Pakistan from June, 2021 to January 2022. Body Mass Index (BMI) was based on weight and height. ABI was measured by a handheld Doppler (V20 Italian 8Mhz). PDN was tested via 10g Monofilament Test (10 points on the feet). HbA1c was analysed from venous blood, in a kit for diabetes. Wagner grading was by anatomical assessment. SPSS v20.2.0 was used for data analysis.*

Results: *Mean BMI was 23.99 ± 4.80 kg/m² (range 15.60-34.90). Mean ABI was 0.571 ± 0.201 (range 0.00-1.20); the cohort had moderate-to-severe PVD; 92% individuals had an ABI indicating arterial disease. Mean 10g MFT result was 2.484 ± 2.251 positive sites (of 10), corresponding to severe PDN; 94% of these patients had peripheral skin changes with neuropathy. Mean HbA1c was 9.581 ± 1.760% (range 7.00-14.50%); 30% had HbA1c >7%, 62% had HbA1c >8% (untreated diabetes). Wagner grade distribution: Grade 0 (1%), Grade 1 (11%), Grade 2 (32%), Grade 3 (33%), Grade 4 (14%), Grade 5 (8%). Multivariate regression identified a negative HbA1c-ABI relationship: this is consistent with the expected higher degree of vascular blockage as ABI falls with higher HbA1c.*

Conclusions: *These clinical data establish that we have a population with end stage, multi-faceted diabetic complications - almost universal peripheral*

neuropathy (94%), mostly moderate-to-severe PVD (92%), and sustained poor glycaemic control (62% with HbA1c >8%). This, together with the inverse/bivariate HbA1c-ABI correlation, confirms glycaemic control as the common upstream cause of vascular and neuropathy-related foot injury among the patients in this population. All diabetes clinic OPDs in Khairpur should adopt standards of clinical screening for PDN and PVD.

INTRODUCTION

Diabetic foot ulcer (DFU) is the end result of a pathologic process triggered by persistent hyperglycemia, and amplified by two main vascular consequences of diabetes - peripheral diabetic neuropathy (PDN) and peripheral vascular disease (PVD). PDN eliminates the protective sensation in the foot, eradicating the pain signal that would normally arouse the patient to respond to insult, injury or pressure. PVD diminishes microvascular flow distal to the site of the ulcer leading to an inability to heal the wound as well as providing a hypoxic milieu, conducive to infection and gangrene. Co-existing pathways - as is the case with many patients with long-lived DMT2 - can transform the minor wound into an amputation event.1,2

Formally assessing the magnitude of these pathways requires testing. Ankle Brachial Index (ABI) - using a portable Doppler device - is a non-invasive test of peripheral arterial blockage. A value below 0.9 indicates PVD, below 0.4 indicates severe limb-threatening ischaemia.3 10g Monofilament Test (10g MFT) is a measure of loss of protective sensation from the 10 sites on the plantar surface of the foot; a response at less than 8 sites indicate peripheral neuropathy and less than 6 sites indicate severe neuropathy (with skin changes).4 HbA1c is a measure of the average glycaemic exposure over the last 2-3 months and a definitive indicator of overall diabetes control, as well as the biochemical marker of the link from hyperglycemia to complications.5 And Body Mass Index (BMI) is a measure of weight status, an important metabolic risk factor for PVD and elevated plantar pressure.

In Pakistan, there is little data on the severity of PDN and PVD from rural centres for patients with DFU. Most data on a national level are from urban tertiary referral hospitals; region-specific variability in the complications burden (due to such factors as diabetes duration, medication availability, dietary habits and other socioeconomic factors) remains poorly understood. Gambat Institute of Medical Sciences (GIMS) in Khairpur, Sindh provides services to the rural, low-income population and therefore data from this health care site is useful in determining the burden of complications in this largely unexplored population.

This is the third paper in a series of four articles based on the MPhil thesis of Farooque Ali Bhatti (University of Sindh, 2022) describing and exploring the clinical investigation data (100 cases) for DFU patients at GIMS Khairpur. Paper 1, Paper 2 and Paper 4 covered social and demography, use of medications and management respectively. It will present the comparative analysis of all the variables in Paper 4.

1.1 Aims and Objectives

(1) to quantify and describe the distribution of BMI in DFU patients; (2) to quantify the severity of PVD using Ankle Brachial Index (ABI) with Doppler; (3) to quantify the severity of PDN in DFU patients using 10g Monofilament Test; (4) to assess the state of glycaemic control, using the HbA1c; (5) to report the distribution of Wagner ulcer grades; and (6) to examine the linear relationship between HbA1c and ABI resulting from glycaemia-induced vascular blood flow impairment.

LITERATURE REVIEW

DFU pathophysiology hinges on dysfunction between chronic glycaemia, PDN and PVD. Chronic hyperglycemia activates a series of biochemical changes (polyol pathway, early and late glycation end-products, oxidative stress and protein kinase C) which in concert injure

peripheral nerve and vascular endothelium.6 Knowledge of the clinical relevance of these changes in DFU patients, as measured by standardized tools, is the basis of risk classification and treatment strategy.

PDN is the most common complication of longstanding DMT2; up to 50% of all diabetics are affected after 10 years of the disease.7 This is commonly distal symmetric polyneuropathy (DSPN), which manifests as loss of protective sensation in the feet with a stocking-glove spread. This is screened for internationally with the 10g Semmes Weinstein monofilament.4 Confirmation of the clinical definition of significant neuropathy is made by loss at fewer than 8 of 10 defined sites on the foot, with fewer than 6 sites defining high risk neuropathy and trophic skin changes. South Asian studies report a high prevalence of significant neuropathy (>70%) in DFU patients at presentation, in line with the advanced nerve damage expected to take place before ulceration occurs.8

The distribution of peripheral vascular disease (PVD) differ in diabetics from that seen in non-diabetics. Whereas non-diabetic PVD has a tendency to affect the aortoiliac and femoral segments, diabetic PVD has a distinctive pattern of involvement of tibial and peroneal arteries between the knee and ankle - vessels responsible for supplying the foot.9 ABI is therefore an important test: a normal ABI (0.9-1.3) excludes significant PVD, while an ABI below 0.9 indicates obstruction and below 0.4 indicates severe ischaemia (CLI and high risk of amputation).3 Pakistan and South Asia studies report an ABI below 0.9 in 60-85% of patients with DFU, and an ABI below 0.5 in 30-50% of patients - a distribution reflective of advanced arteries expected in poorly treated diabetes.10

HbA1c is the most important biomarker for glycaemic control in DMT2. Levels over 7% reflects suboptimally treated diabetes; levels above 8% reflect poor diabetes management and patient compliance. In the UKPDS, every 1% fall in HbA1c decreased the risk of developing a microvascular complication by 37%.11 For DFU in particular, HbA1c above 8% predicts higher initial Wagner grade of the wound, delayed healing times, increased risk of infection and amputations.12 The effect of HbA1c on ABI (depending on the common root cause of hyperglycaemia, namely glycation injury to nerves on one hand, and vascular endothelium on the other) has been shown in multiple regression analyses with higher HbA1C being a predictor for lower ABI.13

BMI is well known to predict DMT2 and the biomechanical factors that contribute to DFU. Higher BMI causes increased load on the plantar surface, leading to callus formation and ischaemia.14 DFU patients in resource poor countries may however not have elevated BMIs, and may have normal or even low BMI secondary to poor nutrition, suggesting that the interpretation of BMI in DFUs in low-income populations is complex.

Wagner system of classification is the most commonly used system to grade the severity of DFU in Pakistan and elsewhere. The six grade (0-5) system is helpful in establishing an anatomical classification of the wound for treatment decisions and prognostication.15 Grade 0 represents pre-ulcerative lesions or healed ulcers; Grade 1, superficial ulcers; Grades 2-3, deep ulcers without and with bone involvement respectively; Grades 4-5, partial and whole-foot gangrene. A higher proportion (Grades 2 and 3) are observed at initial presentation in most DFU cohorts in South Asia, and reflect the sub-optimal point of DFU referral.16

MATERIALS AND METHODS

3.1 Study design and setting

Using a non-selective, consecutive sampling survey design, 100 adults (aged over 18 years) with DMT2 and current or past history (within six months) of active DFU were studied from June 2021 to January 2022 at the OPD of GIMS, Khairpur, Sindh for the MPhil project under the supervision of Prof. Dr. Tahira Jabeen Ursani, Department of Zoology, University of Sindh, Jamshoro.

3.2 Participants
A total of 100 consecutive adult patients with DMT2 suffering from DFU or those who had suffered from DFU in the last six months were recruited via non-selective, consecutive sampling. Inclusion and exclusion criteria are provided in Paper 1 in this series.

3.3 Clinical Measurements
Body mass index (BMI) was derived as weight (kg) divided by the square of height (m^2) (kg/m^2) and classifications were: underweight (<18.5), normal (18.5-24.5), overweight (24.5-30.0) obese (>30.0), and severely obese (>40.0). ABI was calculated by the ratio of to the higher pressure in the foot (as measured using Doppler ultrasound with a 4-8 MHz probe, V20 Italian) to the pressure in the arm (measured with an automated sphygmomanometer on the non-dominant arm). Systolic pressures were measured for the following arteries: posterior tibial, dorsalis pedis and brachial. ABI was defined as foot systolic pressure/brachial systolic pressure; results were classified as: poorly compressible (>1.3), normal (0.9-1.3), mild obstruction (0.7-0.89), moderate obstruction (0.4-0.69) and severe obstruction/PAD (<0.4). A 10g Semmes-Weinstein Monofilament Test was conducted at 10 plantar sites with patient's eyes closed; test results were classified as: low risk (all 10 sites sensitive), medium risk (increased neuropathy, when less than 8 of 10 sites were sensitive) and high risk (increased neuropathy and skin changes, when less than 6 of 10 sites were sensitive). HbA1c was calculated after 5mL of venous blood was collected in an EDTA tube and running a specific diabetic kit, and classified as: normal (4.0-5.6%), prediabetic (5.7-6.4%), diabetic (6.5-7.0%), high range (>7%) and untreated/uncontrolled (>8%). Wagner grading was done by anatomical examination of the foot using Meggit-Wagner grading scale (Grades 0-5).

3.4 Statistical Analysis
SPSS (IBM) version 20.2.0 was used for the analyses. Descriptive statistics are reported as mean ± standard deviation (SD), median, mode and range. All four clinical markers' distributions were plotted in histograms with normal distribution curves. A linear regression was run with the dependent variable: ABI, and independent variable: HbA1c to test the hypothesis that a rise in HbA1c would predict poorer blood flow (decline in ABI).

3.5 Ethical Considerations
All patients were given informed consent. Participants were given anonymity. Approval was sought for the study from GIMS. The protocol of this study was compatible with the Helsinki Declaration.

RESULTS
4.1 Body Mass Index (BMI)
The mean, median, mode, range, minimum, and maximum of BMI of the 100 patients with DFU is shown in Table 1. BMI ranged from 15.60 to 34.90 kg/m^2 with a mean of 23.99 ± 4.80 kg/m^2. The median BMI was 24.15 kg/m^2 and mode was 26.20 kg/m^2 showing that, though the mean is in the normal weight range, the distribution is slightly more skewed towards overweight. The greatest distribution of cases had a BMI of 16-29. None of the patients were morbidly obese (BMI >40 kg/m^2).

4. RESULTS
Table 1: BMI Statistics Among DFU Patients (n=100)

Statistic	Value	Interpretation
Mean ± SD	23.99 ± 4.80 kg/m^2	Normal range
Median	24.15 kg/m^2	Normal-overweight border
Mode	26.20 kg/m^2	Overweight category

Range	15.60 – 34.90 kg/m²	Underweight to Obese
Peak frequency range	16 – 29 kg/m²	Predominantly normal/overweight

Table 1 shows the BMI statistics of the 100 patients with DFU. BMI ranged from 15.60 to 34.90 kg/m² with a mean of 23.99 ± 4.80 kg/m². The median BMI was 24.15 kg/m² and the mode was 26.20 kg/m², suggesting that although the mean is normal, the data is skewed a bit towards overweight and obese. The greatest number of patients had a BMI of 16-29. The study did not have any patients with morbid obesity (BMI >40).

Table 2: ABI Statistics and Peripheral Vascular Disease Severity Distribution Among DFU Patients (n=100)

ABI Category	ABI Range	Frequency (n)	Percentage (%)
Normal arterial pulse	0.9 – 1.3	4	4.0%
Mild arterial obstruction	0.7 – 0.89	4	4.0%
Moderate obstruction (PVD)	0.4 – 0.69	70	70.0%
Severe obstruction / PAD (<0.4)	<0.4	22	22.0%
Mean ± SD	0.571 ± 0.201	—	—
Median	0.595	—	—
Mode	0.52	—	—

Ankle Brachial Index (ABI) details are shown in Table 2. Mean ABI was 0.571 ± 0.201, with a median of 0.595 and a mode of 0.52. The range of ABI was 0.00 to 1.20, with the greatest number of cases falling within the 0.20-0.60 ABI range - well within the threshold of moderate PVD (0.4-0.69). The mode (0.52) is consistent with a high frequency of moderate PVD. None had an ABI greater than 1.3 (badly compressible). Just 4% of patients had normal ABI (0.9-1.3): so 96% had some arterial blockage and 92% had clinically significant PVD (ABI <0.9).

Table 3: 10g Monofilament Test Statistics — Peripheral Diabetic Neuropathy (n=100)

PDN Risk Category	Positive Sites	Frequency (n)	Percentage (%)
Low Risk (all sites positive)	10/10	6	6.0%
Increased Risk — Neuropathy	<8 sites	0	—
High Risk — Neuropathy + Skin Change	<6 sites	94	94.0%
Mean ± SD	2.484 ± 2.251 sites	—	—
Median	2.00 sites	—	—
Mode	0.00 sites (no sensation)	—	—

The statistics for 10g Monofilament Test are reported in Table 3. The average number of positive sites for the sensation was 2.484 ± 2.251 of the 10 sites. The median was 2.0 sites and the mode was 0.0 sites - the highest concentration of cases in the sample had no sites positive (a complete loss of protective sensation in all 10 sites). The frequency distribution curve showed the highest distribution of cases between 0 and 5 positive sites, revealing most of the patients fall into the high risk group of neuropathy (less than 6 positive sites). The conclusion of the thesis is that 94% of patients with DFU had peripheral neuropathy leading to loss of sensation and skin changes.

Table 4: HbA1c Statistics and Glycaemic Control Distribution Among DFU Patients (n=100)

HbA1c Category	HbA1c Range	Frequency (n)	Percentage (%)
Controlled Diabetes	6.5 – 7.0%	8	8.0%
High Range (Uncontrolled)	>7.0%	30	30.0%
Untreated / Severely Uncontrolled	>8.0%	62	62.0%
Mean ± SD	9.581 ± 1.760%	—	—
Median	9.35%	—	—
Mode	9.70%	—	—

HbA1c is reported in table 4 below. Mean HbA1c was 9.581 ± 1.760%, with a median of 9.35% and a mode of 9.70%. Most cases (peak frequencies) were found between 7% and 11% HbA1c. The frequency demonstrates: 30% of the DFU patients had HbA1c >7% (uncontrolled diabetes, Grade 0 and 1 ulcers predominating); 62% had HbA1c >8% (untreated/severely uncontrolled diabetes, higher grade ulcers); and 8% had HbA1c <7% (relatively controlled diabetes, Grade 0 and 1 ulcers only). No patient was normal/prediabetic at the time of the study.

Table 5: Wagner Ulcer Grade Distribution Among DFU Patients (n=100)

Wagner Grade	Description	Frequency (n)	Percentage (%)
Grade 0	Pre/post-ulcerative lesion (healed)	1	1.0%
Grade 1	Superficial ulcer (partial/full thickness)	11	11.0%
Grade 2	Deep ulcer, no bone involvement	32	32.0%
Grade 3	Deep ulcer with bone involvement	33	33.0%
Grade 4	Forefoot / partial foot gangrene	14	14.0%
Grade 5	Whole-foot gangrene	8	8.0%
Total		100	100.0%

The distribution of Wagner ulcers in all 100 patients with DFU is shown in Table 5 above. Combined Grade 2 and 3 (deep ulcers either not involving bone, or deep ulcers that extend to bone, respectively) was present in 65% of patients, confirming that most presented with deep ulcers. 14% had Grade 4 (forefoot gangrene) and 8% had Grade 5 (whole-foot gangrene), with 22% having both Grade 4-5 (frank gangrene). At follow-up only one patient (1%) had heal to Grade 0 and 11% had Grade

Table 6: Summary Statistics for All Four Clinical Risk Factor Variables (SPSS Table 4.3 from Thesis)

Statistic	BMI (kg/m²)	ABI	10g MFT (sites)	HbA1c (%)
N Valid	100	100	100	100
Mean	23.991	0.572	2.484	9.581
Median	24.15	0.595	2.00	9.35
Mode	26.20[a]	0.52	0.00	9.70
Std. Deviation	4.801	0.201	2.251	1.760
Range	19.30	1.00	10.00	7.50
Sum	2399.10	57.19	248.40	958.11

Linear regression of HbA1c (independent variable) with ABI (dependent variable) showed a statistically significant decrease in ABI with increasing HbA1c (Figure 4.16 in parent thesis). It demonstrates that deterioration of HbA1c is clearly linked with increasing peripheral artery occlusion in this group. The regression supports the view that hyperglycemia is the underlying common trigger for glycation-related neuropathic changes and also the vascular occlusion.

DISCUSSION

The data presented in this paper on the clinical investigation of the cohort paint a picture of severe multi-dimensional diabetic complications in all four areas: almost All (94%) suffer from peripheral neuropathy, mostly at the moderate-severe grade (92%) of PVD, are chronically bad glycemic controls with 62% HbA1c over 8%, and have a skewed distribution of ulcer grade, largely at the more complicated stages (65% Grade 2-3, 22% Grade 4-5). Collectively, the results place in clinical context the epithelial failure (responsible for the inhibiton of insulin secretion) and behavioural failure (responsible for the neglect of other medical interventions - an increase in medication, health check-ups, and lifestyle changes) reported in this series of papers (Paper 1 and 2), and that can be visibly quantified and in many cases irreversibly damaged to the tissues.

5.1 BMI: Mean is Normal, But Don't be fooled

This mean BMI of 23.99 ± 4.80 kg/m² is in the normal range, and might superficially imply that obesity is not a significant challenge in this group with DFU. But we must be careful in such an interpretation for two reasons. First, the mode BMI of 26.20 kg/m² and the median of 24.15 kg/m² suggest that the groups of patients who suffer from DFU skew towards overweight and the BMI range (15.60-34.90 kg/m²) covers all patients from underweight to obese and would reflect the socioeconomic diversity in the cohort rather than a single value of mean. Second, for South Asians the metabolic complications related to BMI occur at lower cut-offs than for Westerners. The WHO has proposed to lower the BMI cut-offs for obesity in the Asian region - overweight at BMI>23 kg/m² and obesity at BMI>27.5 kg/m² - as South Asians develop central fatness and its metabolic complications in the lower range of BMI.17 Applying these Asian-specific cut-offs, the mean

BMI in this group of 23.99 kg/m² is at the cusp of the Asian overweight cut-off, and more patients would be classified as metabolically risked than reported by the conventional WHO cut-off points. Foot pressure - rather than full-body BMI - is the more clinically-relevant factor for DFU. The higher plantar pressures over the metatarsal heads of obese and overweight patients with neuropathy is a major cause of callus and ulcer formation. Even with a normal BMI, the combination of neuropathy and a BMI in the overweight category (BMI ≥ 25) can result in abnormally high plantar pressures (especially with bad footwear as contributing factor). The data in Paper 1 that 77.27% of immobile, dirty patients had callus ulcers are consistent with this mechanism for BMI levels below the usual BMI cut-offs for obesity.

5.2 ABI: A Population in Severe PVD

The results in the ABI are most disturbing. A mean ABI of 0.571 puts the "average" DFU patient in the moderate obstruction category and the mode of 0.52 suggests moderate-to-severe PVD is the most common clinical presentation. This is further reflected in the distribution of ABIs: 70% of patients had an ABI 0.4-0.69 (moderate obstruction) and 22% had an ABI below 0.4, the cut-off for severe PAD/critical limb ischaemia. Just 4% of patients had normal ABI values, with 96% having narrowing of their arteries (pausing flow and pressure) and 92% having clinically significant PVD.

This is more than reported from DFU patients from urban centres in Pakistan where PVD prevalence of 60-70% is more common.10 These higher rates of PVD in the Khairpur cohort can be attributed to the interaction of poor glycaemic control (mean HbA1c 9.58%, Paper 1) and high smoking prevalence (49% habitual, Paper 1) with the delay in seek specialist care described in Paper 2. This is because smoking promotes endothelial dysfunction and rapid development of atherosclerosis; unchecked hyperglycaemia promotes protein glycation and oxidative damage to the blood vessels; and the delays in time to consultation (Paper 2) allow these processes to continue for months or years prior to medical assessment.

These ABI test results have important clinical implications. In patients with ABI <0.4 (22% in this cohort) there is critical limb ischaemia and no wound (even of slight depth) will heal without vascular intervention. Wound care, antibiotics and debridement may be all that can be offered for these patients, and primary care involves revascularisation (angioplasty or bypass surgery) or, if this fails, amputation at the most distal possible level. The thesis does not mention the availability of vascular intervention (surgical or interventional radiology) at GIMS or other district level hospitals in Khairpur, but the large proportion of severe PAD patients in this study suggests a need for specialist vascular surgery or interventional radiology services at the tertiary level in the region.

The 22% of patients with ABI <0.4 with Grade 3-5 ulcers with a hissing Doppler (nearly complete artery occlusion) present the biggest challenge. In this group of patients the triad of absent protective sensation (mode MFT = 0 sites), critical ischaemia and gangrenous or deep ulceration leads to the high probability of conservative healing failure. An early diagnosis for this subgroup using routine Doppler ABI measurements is therefore not an improvement in care - it's a triage decision: to first realise this sub-population facilitates early referral to vascular surgeons to apply definitive therapies, rather than protracted wound care.

5.3 10g Monofilament Test: Essentially All Patients Have Loss of Protective Sensation

The 10g MFT test findings represent the highlight of this paper: Most commonly - that is, the mode - was 0.0 positive sites, or no protective foot sensation. With a mean of 2.484 positive sites out of 10 sites tested, 94% of the patients classified with high risk neuropathy (less than 6 positive sites), loss of protective sensation is effectively universal in the patients in this DFU paper. This has two important consequences: the patients in this cohort can't be depended on to sense injury to their feet, or to assess the progression of their wounds, or respond to early wound development

via the usual feedback of pain. So all of their foot care must be placed in the hands of others: parents, health professionals or the hospital clinic; their own personal alarm system is missing.

The combination of severe neuropathy and severe peripheral vascular disease (PVD) in most patients in this group marks the neuroischaemic DFU phenotype - which is known as the hardest-to-heal and most-liable-to-amputate DFU type.18 In a neuroischaemic ulcer, the warning system is removed by neuropathy and the healing system is removed by PVD; the ulcer is not painful enough to motivate the patient to seek care and the blood flow to the tissue is not adequate for granulation tissue formation and re-epithelialization. The Wagner Grade 2-5 axis predominance (89%) in this study is the clinical signature of this neuroischaemic DFU.

The 10g MFT is internationally recommended as an annual test for all patients with diabetes, and has the capacity to identify the high-risk foot.4 The fact that 94% of patients in this study presented in the high-risk (neuropathy) category, without having been identified, is an indication of its absence from the general practice and district hospital-based diabetes consultations in Khairpur. The 10g MFT kit is very affordable (PKR 500-1000) and has no power or training requirements. There is no cost or technology barrier to its inclusion and use in the diabetes assessment in Pakistan.

5.4 HbA1c: Biochemistry of a 10-year Undertreatment

The HbA1c results make a cogent and sobering story. The average value of 9.581%, 62% of the patients having HbA1c above 8% (untreated, or severely under treated diabetes), and with 8% having HbA1c below 7% controlled diabetes, is one of severe ongoing hyperglycaemia in the population studied over the course of their disease. The distribution of HbA1c values (7.00-14.50%) spans the silver-to-gold-taps' gamut from poorly to horrifically poorly controlled diabetes, skewed towards the latter end.

The linear regression of HbA1c on ABI - showing that increasing HbA1c is associated with decreasing ABI - bridges the link. Prolonged hyperglycemia results in protein glycation, formation of advanced glycation end-products (AGEs) and stiffening of the vascular wall endothelium, smooth muscle cell dysfunction and the more rapid formation of peri-arterial atherosclerotic plaques in the lower limb. At the same time, hyperglycemia activates the polyol pathway in peripheral nerve axons - thereby depleting the compound myoinositol and decreasing the nerve's ability to conduct impulses - leading to progressive sensory dysfunction, measured here by the 10g MFT.6 The HbA1c-ABI regression therefore describes, not just a statistical relationship, but a mechanistic link: the greater the lifetime exposure to hyperglycemia, the greater the endothelial glycation, the lower the ABI, the worse the ischaemic environment in which the wound develops.

The takehome message is clear: better control of HbA1c is not just a theoretical, statistical target HbA1c but a real, tangible intervention that if achieved, retards the progressive decline of ABI and neuropathy to reduce the grade of ulcers seen in future patients. The UKPDS quantifies the relationship - every 1% drop in HbA1c reduces risk of microvascular complications by 37%.11 Presumably, in this cohort with mean HbA1c of 9.58% (target 7%) this represents a 50-70% reduction in microvascular complications with a 2.5% reduction in HbA1c, as is achievable with combination pharmacotherapy, not a disease-modifying paradigm that any dressing or surgical intervention can match.

5.5 Wagner Grade: Summary of Multiple Failure

The distribution of Wagner grades (65% Grade 2-3 and 22% Grade 4-5) is the clinical correlation of all the failures of diabetes management described in the previous papers: poor medication (Paper 2), poor attendance (Paper 2), poor referral (Paper 2) and virtually universal neuropathy and PVD described in this paper. These Grade 2-3 ulcers represent lesions that have advanced beyond the superficial layers of the skin into the deep soft tissues, or almost to bone - the lesions that would have been detected and treated in a diabetic foot

service (Grade 0-1) with an annual foot screening program. Grade 4-5 ulcers - gangrene - represent wounds that were not detected at all so that gangrene developed.

The rate of gangrene (Grade 4-5) ulcers in this population (22%) is higher than most urban DFU services in Pakistan (10-15%), and possibly reflects the culmination of rural barriers to care, high burden of PVD, time delay to seeking Hakeem care, and the almost universal absence of protective foot sensation.16 These patients represent the "terminal event" outcome of the failures described across this series - and the most costly, clinically and financially. The annual cost of preventing a DFU (Dracula foot screening and HbA1c monitoring, medication titrations and titrations, diabetic foot hospital admission, surgery, and rehabilitation) greatly exceeds the cost of annually screening a patient for DFUs and monitoring HbA1c and adding medications when needed.

CONCLUSION

This is the first diagnostic study of the level of disease complication among DFU patient at rural Sindh, Pakistan, using the four standardised clinical tests - body mass index (BMI), ankle-brachial index (ABI), 10g filament monofilament test and HbA1c - along with Wagner grading. Our results show that this population is indeed severely, and comprehensively diseased - 94% peripheral neuropathy, 92% severe PVD, 62% untreated hyperglycaemia, and 87% advanced ulceration (Grade 2-5). The case is made that persistent diabetic hyperglycemia drives both the vascular blockage and neuropathic damage in this community by the inverse HbA1c-ABI regression.

This study suggests urgently the need in Khairpur to incorporate the measurement of ABI and 10g Monofilament sensation testing in every diabetes clinic visit, and the escalation of medication based on HbA1c levels as described in Paper 2. The early detection of high-risk neuropathy and PVD, while the foot remains intact is the only way to obviate the Grade 3-5 presentations that are the predominant ones in this patient population that suffers amputation, long-term hospital stays and uncorrectable socioeconomic disfiguration of the affected families.

Study limitations include the cross-sectional (single site) nature of the study, with no follow-up after the evaluation, and lack of nerve conduction velocity studies or angiography, which would allow more accurate definitions of neuropathy and vascular disease. Further studies with prospective clinical and vascular imaging follow-up are encouraged.

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