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Factors associated with ulcer healing and quality of life in patients with diabetic foot ulcer.

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Original Article

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Abstract:

A prospective non-randomized cohort study on consecutive diabetic patients with foot ulcer was undertaken, to assess factors associated with the healing process or limb salvage, and evaluated the impact of their treatment on their quality of life (QOL). QOL was evaluated using diabetic foot ulcer scale-short form questionnaire (DFS-SF) before and after treatment. A total of 103 diabetic patients with ulcer (mean age 69.7±9.6 years, 77% male) were treated and followed up for 12 months. Ulcer healing, minor amputation and major amputation rates were 41, 41 and 18%, respectively while mortality rate was 18%. Ulcer healing was associated with University of Texas wound grade I and the SIDESTEP trial's diabetic foot infection wound score. Limb loss was associated with non-palpable popliteal artery, longer in-hospital stay and delay until referral. QOL was improved in all domains of DFS-SF ($p<0.0001$) throughout the cohort of our patients regardless of their outcome and no outcome (healing, minor or major amputation) was superior to other. Significant improvement was observed in all domains of hygiene self-management after consultation during follow up period.

Key words: Diabetic foot; ulcer; quality of life; limb loss.

Introduction

The International Diabetes Federation (IDF) reported that the global prevalence of diabetes (DM) in adults was 8.3% in 2013 expecting to rise beyond 592 million by 2035 with a 10.1% global prevalence.[1] One of the most insidious complications of DM is foot ulcer and according to the World Health Organization (WHO), all foot complications may be encompassed under the term DFS (diabetic foot syndrome) defined as "ulceration of the foot associated with neuropathy and different grades of ischemia and infection."[2] DFS was always a multinational burden and in recognition of this reality the St. Vincent Declaration in 1989 included a set of goals for the health care of people with DM.[3] In response to the emerging pandemic of DM type 2, after this declaration, several other regional partnerships between the IDF and WHO, proceeded with their own declarations such as: the Declaration of the Americas or DOTA (1996),[4] the Western Pacific Declaration on Diabetes (WPDD 2000)[5] and the Declaration and Diabetes Strategy for Sub-Saharan Africa (2006).[6]

Various wound classification systems have been developed, so there will be a common 'language' among the physicians and a helpful tool in the planning and monitoring of treatment and in predicting the outcome of ulcer healing and assessing the associated factors.[7,8,9,10,11] Many practical guidelines have been published with most recent one the evidence-based global consensus for the prevention and management of diabetic foot by the International Working Group on the Diabetic Foot (IWGDF) Editorial Board.[12]

Along with increased morbidity, foot ulcers can lead to lifelong disability and may substantially diminish the quality of life (QOL) for these patients.[13] Specifically, patients with DFS have restrictions on mobility, poor psychosocial adjustment, and lower self-perceptions of health than patients who do not have ulcers.[13,14] An

understanding of the specific effects of DFS on individual patients' QOL is central to the direction of treatment, adherence to treatment, and patient/practitioner communication.

The aim of this observational study was primarily to assess the factors associated with the healing process or limb salvage in diabetic patients with foot ulceration. We also evaluated the impact of treatment and QOL outcomes.

Methods

A prospective non-randomized cohort study on consecutive diabetic patients with foot ulceration was undertaken in a Mediterranean country (Central Greece, an area with mainly agricultural production) by a tertiary centre which has the only existing foot clinic service in the region. These were patients with DM type 2 suffering from lower limb ulceration who were referred to our service either at the outpatient clinic or as an emergency. Exclusion criteria were: i) malnutrition (body mass index: BMI< 18), ii) immobility (bed or wheel chair bound or stroke limb), iii) immune-suppression, and, iv) lacking mental capacity to consent to the study.

The patients were under close follow up since their first assessment and had regular appointments in the outpatient clinic of our service depending on their ulcer healing progress. On the first visit, demographics (age, sex, height, weight, body mass index-BMI) and personal details (residence address, occupation, carer identity) and the past medical history, including duration of DM, history of hypertension (HT), hyperlipidemia (HL), coronary artery disease (CAD), atrial fibrillation (AF), peripheral artery disease (PAD), chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), cerebrovascular disease (CVD), ophthalmopathy, history

of smoking and alcohol, antiplatelet and statin therapy were recorded. Additionally, family history of HT, HL and DM was also recorded.

In addition, all patients received clinical assessment by a Vascular Surgeon, including palpation of the peripheral arteries, Ankle brachial index (ABI) measurement, ulcer evaluation and a recording of self-management hygiene (self-examination, foot washing, foot hydration, the way of cutting their nails, walking barefoot and usage of special anatomical shoes). Ulcer evaluation was undertaken according to three grading systems: i) the University of Texas wound classification which is a system for diabetic foot wounds that evaluates wound depth, the presence of infection, and peripheral arterial occlusive disease in every category of the wound assessment,[9] ii) the diabetic foot infection (DFI) wound score based on SIDESTEP trial (Study of Infections in Diabetic feet comparing Efficacy, Safety and Tolerability of Ertapenem versus Piperacillin/tazobactam) with the measurement of 10-items,[10] and, iii) the Society for Vascular Surgery developed a Lower Extremity Threatened Limb Classification System in which the risk stratification is based on 3 major factors that impact amputation risk and clinical management such as wound, ischemia and foot infection (WIfI).[11] The goal of all these systems is to improve communication, leading to a less complex, more predictable treatment course and, ultimately, an improved result.

Additionally, neuropathic pain (NP) was also assessed using LANSS (Leeds Assessment of Neuropathic Symptoms and Signs) scale questionnaire.[15] Patient replies to the questions were a “yes or no” type and were evaluated differently depending upon the question. For this purpose we used the Greek validated LANSS questionnaire.[16]

Since this is an observational study, each Vascular Surgeon could decide on the diagnostic investigations needed [foot X-Ray, Duplex scan, Computed Tomography Angiography (CTA), Digital Subtraction Angiography (DSA)] and on the type of treatment (open surgery, endovascular, hybrid procedures or conservative). Primary outcomes were ulcer healing and minor or major amputation. Analysis of the factors associated with the primary outcomes was undertaken. Secondary outcomes were the impact in QOL after each type of treatment and self-management at 12-month follow up.

A multidisciplinary approach program was established in our hospital regarding these patients.

Regarding the assessment of patient QOL, we used the Greek version of Diabetic Foot Ulcer scale- short form (DFS-SF) as translated by Mapi Research Trust-All (Copyright © 2015 rights reserved).[17] The DFS was developed to measure the impact of diabetic foot ulcers on QOL issues most important to patients. The DFS was also translated into several languages using both forward and backward translations and cognitive debriefing to ensure cultural equivalence. The DFS contains a total of 64 items, 58 of which are used to compute 15 QOL subscales.[18] The 6 remaining items address employment-related issues and are not included in computation of subscale scores on the DFS long form.

The final version of the DFS-SF (short-form)[17] which is used broadly contains a total of 29 items grouped into six subscales:

- Leisure (5 items)
- Physical health (5 items)
- Dependence/daily life (5 items)
- Negative emotions and worried about ulcers/feet (10 items)

- Bothered by ulcer care (4 items)

Thus, each patient had to fill the DFS-SF questionnaire during the first examination, and after 12 months of follow up. Also, the QOL was analyzed in respect to the ulcer treatment, the patient's residence and the level of their home care. Additionally, Visual Analogue Scales for the impact of pain on daily living activities of (VAS-ADL) (0–10) and a 10 cm visual analog scale for the pain intensity (VAS-INT) (0, no pain; 10, unbearable pain)[15] were recorded at their first visit to the outpatient clinic and their last one.

This study involved the collection of existing data and diagnostic tests that have been recorded in such a manner that subjects could not be identified, either directly or through identifiers linked to the subject. However, the protocol and informed consent were approved by the Institutional Review Board.

Statistical analysis

The relationships of categorical variables and the main outcomes observed (ulcer healing, minor amputation, major amputation, mortality) was examined with the use of the Chi Square statistic, while the relationships between main outcomes and continuous measurements was assessed with the independent samples t-test or the Mann Whitney test, where appropriate. The findings were assessed and the statistically significant variables were entered in a binary logistic regression model. The two way interaction effects were also considered to reach the final model for each outcome. For the change in the Quality of life Measures the Paired samples t-test was applied for each of the dimensions measured. Statistical significance was set at 0.05 (two-sided). The analysis was carried out with the use of SPSS v.21.0

Results

Over a period of 2 years (2012-2014) 103 consecutive patients with diabetic foot ulcer entered into the study and were followed up for 12 months. Only 2 patients were already excluded due to the exclusion criteria. The mean age of the patients was 69.7±9.6 years and most of them were males (76.7%, 79/103). More than half of the patients were manual workers and almost everyone was cared for by family members. The population was overweight with mean BMI of 28. Most of the patients were on antiplatelet (80%) and statin (70%) therapy, while half of them were also on insulin. Social-demographics, past-medical history details and blood test results are presented in table 1.

Almost half of the patients (47%, 49/103) presented directly to our hospital as an emergency, while 20% (21/103) were referred by an endocrinologist, 11.5% (11/103) by a general surgeon, 11.5% by a general practitioner (GP), 3.8% (4/103) by another vascular surgeon, 3% (3/103) by an internal medicine physician, 2% (2/103) by a nephrologist, 1% (1/103) by a neurologist and 1% (1/103) by an orthopedic department. The mean time until referral to our service was 23.8±9 days. There was no difference between patients with self-referral and physician referral. However, there was a seasonal variation in the presentation and referral of these patients to our service peaking in colder months during the year (autumn and winter, 64%, 66/103 *vs* spring and summer 36%, 37/103, $p< 0.05$). The most common cause of ulcer was trauma (lack of attention 68%, 70/103; shoe wearing trauma 11.7% ,12/103); after great saphenous harvesting 2% (2/103); after nail cutting 1% (1/103); and 17.5% (18/103) by unknown cause. The ulcers were confined mainly to toes (64%, 66/103), and less frequently to the shin (9.7%, 10/103), the sole (7.8%, 8/103), the heel (7.8%,

8/103), the dorsal surface of the foot (5.8%, 6/103), the ankle (2.9%, 3/103) and in a previous amputation stump area (1.9%, 2/103) (Figure 1).

In table 2 patients are categorized according to the University of Texas wound classification system (i) and according to the Lower Extremity Threatened Limb Classification System (WIfI) (ii). Additionally, the mean DIF wound score was 20.4±3, while the mean LANSS score was 20.5±3.4 (all patients in our study had LANSS score > 12).

During 12 month of follow up, 41% (42/103) of the patients had their ulcer healed. From this group, 40.5% (17/42) of the patients were healed in the first month, 85.7% (36/42) in first 3 months and 97.6% (41/42) in first 6 months. A further 50.5% (52/103) of the patients underwent a minor amputation, 63% (33/52) of which during first hospitalization, 88.5% (46/52) during first 3 months and 98% (51/52) during first 6 months after initial presentation. All but 9 patients achieved healing of their minor foot amputation. These 9 patients along with another 9 underwent major amputation accounting for a 17.6% (18/103) limb loss. Most of the amputations (14/18, 77%) were undertaken in first 6 months.

After multiple logistic regression analysis including characteristics of tables, referral characteristics and ulcer location and causes, ulcer healing was associated with University of Texas wound classification and DIF wound score. Patients with TEXAS grade I ulcer had 23-fold more often ulcer healed (95% CI 2.3-220, p=0.007) than those with a higher grade. Additionally, after increase of one DIF score unit, the odds risk for ulcer non-healing is increased by 15% (95% CI 1.5-30%, p=0.028), with mean DIF score 17±2 for ulcer healed patients and 24.5±3 for non-healed patients. (Figure 2)

Minor amputation was associated with Texas classification, COPD and LANSS score. Patients with TEXAS grade II or higher had 11.3 increased odds risk for minor amputation (95% CI 3.4-38, p<0.001) than those with grade I. Additionally, patients with COPD had 12.3 increased odds risk for minor amputation (95% CI 2.1-73 p=0.006), while for every increase of one unit of LANSS score the odds risk for minor amputation is increased by 43% (95% CI 2-100%, p=0.040). (Figure 3)

Major amputation was associated with palpable pulses of popliteal artery, hospital stay and time until referral. Every patient with non-palpable popliteal artery had 5.2 increased odds risk for major amputation (95% CI 1.03-26 p=0.045). For each additional hospital stay the odds risk for a major amputation increased by 8% (95% CI 2-14% p=0.007). Finally, for each additional day of delay until referral the odds risk for major amputation increased by 3.5% (95% CI 1-6% p=0.011).

Among patients with evidence of ischemia requiring revascularization, no differences were observed in respect to healing rate, minor and major amputation according to the type of intervention; 36 patients underwent 38 procedures: 20 endovascular only, 9 open only and 9 hybrid ones and the total healing rate was 30.5% (11/36). In patients who were not considered candidates for revascularization (67/103), a reasonable healing rate was observed (46%, 31/67).

Lack of multidisciplinary assessment was observed in a large number of patients and therefore during their initial hospitalization they were referred for evaluation to other services: 65 (63%) patients to Endocrinology for DM control, 34 (33%) to Cardiology, 8 (7.7%) to Nephrology, 8 (7.7%) to Ophthalmology, 6 (5.8) to Orthopedics, 4 (3.8) to a Chest Medicine and 1 (1%) to Neurology.

The mortality rate was 17.5% (18/103) during the 12 month period. Myocardial infraction (MI) accounted for the majority of deaths (72%, 13/18), while 3

patients died because of severe sepsis and 1 due to acute renal failure. After multivariate analysis only age was associated with death. For each one additional year of age, the risk of death was increased by 17% (95% CI 7 -29% p=0.001). During 12-month follow up no patient had a development of a new ulcer or a deterioration of a healed one.

All alive in 12 month-follow up patients completed the QOL questionnaire (DFS-SF) in their first and the last assessment (12-month follow up); 82.5% (85/103) were available for QOL assessment at 12-month follow up. QOL was significantly improved in all domains of DFS-SF ($p<0.0001$) throughout the cohort of our patients after their treatment as compared with their condition before treatment. (Table 4) In addition, after further analysis, it appeared that the improvement of QOL was not associated with the type of treatment and the outcome, thus there was no difference in improvement of QOL among patients regardless of whether they had their ulcer healed or had undergone an amputation. The lower improvement in QOL was demonstrated in domains related to physical health (mean increase 9.9), dependency in daily life (mean increase 10.9), treatment satisfaction (mean increase 12.4) and higher improvement in domains related to leisure (mean increase 16.5) and negative emotions (mean increase 18.2). Finally, when QOL was analyzed according to the patient residency area and the caring person, no correlation was identified. A significant improvement was observed in all domains of hygiene self-management between the first and the last assessment (12 months) of follow up while VAS of both types were improved significantly during follow up.(Table 3)

Discussion

In our study, the mean duration of DM among patients was 18 ±3 years. However, it was demonstrated that their actual awareness about the nature of the disease was inadequate. Thus, 50% of our patients presented to our service late from the onset of the ulcer (mean time 24 days), with a poorly controlled DM (mean Hb1AC: 8.1% and BMI: 28) and low awareness of hygiene self-management (table 3). It has been previously demonstrated that foot self-care is generally infrequent, and clinical monitoring in outpatient clinics is performed for less than half of diabetic patients with foot ulcers.[19] In practice, patient education aiming to promote foot care knowledge and self-examination is advocated by most experts and guidelines as an important strategy to prevent diabetic foot complications. Education of patients at high risk of or with ulceration is considered to be particularly important.[20] In some trials, foot care knowledge and self reported patient behavior seem to be positively influenced by education in the short term.[21] In our study after many consultations of our patients during follow up, they managed to improve their hygiene self-management status considerably (Table 3), decreasing the likelihood of a new ulcer. However, the effect of patient education is still in doubt and there is insufficient robust evidence that limited patient education alone is effective in achieving clinically relevant reductions in ulcer and amputation incidence.[21] Additionally, in our study, almost half of the patients had a late referral by their physician, and thus it would seem advisable to implement strategies oriented towards the improvement of primary care physician awareness of diabetic foot and its complications, along the IWGDF recommendations that healthcare professionals should receive periodic education to improve the care of high-risk individuals.[12] It is true that such patients may neglect themselves because of various reasons including impaired sensation due to neuropathy, impaired vision as a result of retinopathy, and other co-morbidities

including cardiac and renal impairment which all may contribute also to the lack of a personal alarm system.[22,23]

It is still debatable whether ulcer healing in diabetic patient always requires revascularization. Although, in a recent systematic review, it was demonstrated that improved rates of limb salvage were associated with revascularization compared with the outcomes of conservatively only treated patients, there were insufficient data to recommend one method of revascularization over another.[24] Along this line, in our study, no differences were observed in respect to healing rate, minor and major amputation according to the type of intervention. However, this was an observational study and not designed to compare those treatments. Over the last decade, there has been a marked shift from open revascularization to an endovascular one in diabetic patients with foot ulcer[25]and in some centers endovascular treatment is used first as "preliminary approach" for critical limb ischemia and diabetic foot.[26] Additionally, in patients who were not considered candidates for revascularization, a reasonable healing rate was observed (46%, 31/67). Recently, it was suggested that even diabetic patients with ischemic foot ulcers not available for revascularization, should not be excluded from healing without major amputation.[27]

The SIDESTEP trial has demonstrated that the clinical response was less favorable at the follow-up assessment in patients with a DIF score >19.[10] Along this line, our study showed that patients with healed ulcer had a score of mean value 16.8 (figure 2). Another important factor that was associated with ulcer healing was the TEXAS classification during first examination. Thus, it seems that initial clinical evaluation with the use of DIF score and TEXAS classification may help physicians to identify which patients are at increased risk for non-healing ulcers or even limb loss, and in whom closer follow up and more aggressive treatment may be indicated.

As far as the predictive factors associated with limb loss are concerned, it has been previously demonstrated that male gender and the presence of neuropathy,[28] Severity of Diabetic Foot Infection,[29] elevated fasting blood sugar,[30]WBC and PAD,[31]are associated with amputations. In our study, Texas classification, COPD and LANSS score were associated with minor and delay of hospital referral, the severity of PAD, and the prolonged hospitalization were associated with major amputation. It seems that detailed initial clinical assessment and fast-track management of DFS are important factors associated with limb loss. Furthermore, it is of note that the majority of deaths in our cohort were cardiac related. This underlines the importance of cardiovascular disease risk factor control as primary prevention in patients with DM 2 as it has been recommended from the American Heart Association and the American Diabetes Association.[32]

The evaluation of the patient QOL has been recognized as an important area of scientific knowledge, since the concept of QOL has been related to the notion of health: satisfaction and well-being in the physical, psychological, socio-economic and cultural spheres.[33] According to the WHO, QOL can be defined as an individuals' perception of their position in life in the context of the culture and value systems in which they live in and in relation to their goals, expectations, standards and concerns.[34] Studies have evaluated and reported on QOL in diabetic patients with ulcer and compared them with other control groups.[13,34-38] Presence or history of diabetic foot ulceration has been proved to have a large impact on physical functioning and mobility.[38]Diabetic foot ulcer patients had much worse health related QOL (HRQL) compared with the diabetes population and the general population, especially in physical health.[13, 36-38] Our study is the first to our knowledge that evaluates the QOL in the same group of patients before and after treatment. Thus, in

our study the presence of diabetic foot ulcer was associated with poor QOL, and QOL was significantly improved in all domains of throughout the cohort of our patients after the ulcer management. However, it was interesting, that QOL was improved regardless of patient outcome (healing, minor or major amputation) and no outcome was superior to another. Similarly, VASs were improved after treatment in our cohort. Even in cases that a major amputation was undertaken, the patients perceived their situation as improved in terms of QOL. A recent report was in agreement with that outcome, suggesting that clinicians should not assume that patients will experience poorer QOL outcome only because they underwent an amputation.[34] An understanding of the specific effects of chronic diabetic foot ulcers on individual patient QOL is central to the direction of treatment, management of compliance, and patient/practitioner communication.

Patients with a diabetic foot ulcer should to be assessed holistically, thus intrinsic and extrinsic factors should be addressed and managed by a multidisciplinary diabetic foot team (MDFT) of physicians as soon as possible (within one working day of presentation or even immediately in the presence of severe infection).[12,39,40] However, in many hospitals not only in our country, but also in the Mediterranean region,[41] a MDFT approach has not been adopted and physicians have to work as individuals on diagnosis and management and attempt to refer patients to other specialties when they consider that it is necessary. Studies, have demonstrated that the introduction of a MDFT has been associated with a reduction in the incidence of major amputations in patients with DM. [42,43]

Potential selection and treatment biases may exist as about 50% of patients had PAD, because this study was a prospective observational one, in patients referred to the Vascular Service of a tertiary Hospital. However, this reflects the real world

practice of a Vascular Service which inevitably is committed to deal with more difficult-to-heal ulcers.

Conclusions

Our observational study showed that delayed hospital referral, prolonged hospitalization and absence of popliteal pulses were associated with limb loss. Additionally, initial clinical status assessment with DIF score and TEXAS classification may predict ulcer healing. QOL improved in all patients after treatment regardless of the outcome (healing or amputation). Also, improvement was observed in the hygiene self-management.

No conflict of interest.

Author contribution

All authors contributed to: (1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, and, (3) final approval of the version to be published.

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Socio-Demographics		Past medical history		Blood test	
Sex	76.7% Males (79/103)	**Type of Diabetes**	100% Type 2		Mean±SD
Age in years	69.7±9.63	Mean duration of DM in years	17.7±7.9	**Hb**	11.9±1.7g/dL
Mean height in cm	164.7±24.4	**HT**	93.2% (96/103)	**WBC**	13±3 10^3/µL
Mean weight in kg	79.23±16.7	**CAD**	55.3% (57/103)	**Neu**	72.8±9.5%
Mean BMI in kg/m^2	28±5.1	**AF**	12.6% (13/103)	**PLT**	277±111 10^3/µL
Residency		**PAD**	53.4% (55/103)	**MPV**	8.6±1.2 fL
Urban	53.4% (55/103)	Mean ABI R	0.9±0.3	**ESR**	36.8±20.3mm/h
Countryside	46.6% (48/103)	Mean ABI L	0.7±0.2	**CRP**	4.9±2.4mg/dL
Occupation		Patients with non-compressible ABI	29% (30/103)	**Cr**	1.0±0.3mg/dL
White collar worker	25.2% (26/103)	DSA	38.8% (40/103)	**Ur**	45±26mg/dL
Manual worker	54.4% (56/103)	CTA	2% (2/103)	**Na**	137.2±14mmol/L
Unemployed	20.4% (21/103)	**CRD**	20.4% (21/103)	**K**	4.6±1.2mmol/L
Home carer		**HL**	74.8% (77/103)	**ALT**	24±24 IU/L
Spouse	46.6% (48/103)	**COPD**	11.7% (12/103)	**AST**	28±25 IU/L
Descendants	47.6% (49/103)	**CVD**	12.6% (13/103)	**CK**	106±97U/L
Alone	5.8% (6/103)	**History of alcohol consumption**	23.3% (24/103)	**LDH**	202±92IU/L
Family history of DM	44.6% (46/103)	**History of smoking**		**Bilirubin**	0.5±0.3mg/dL
Family history of PAD	15.5% (16/103)	No	27.2% (28/103)	**Total Chol**	167±52mg/dL
Family history of CAD	76.7% (79/103)	Yes	25.2% (26/103)	**Trig**	168±73mg/dL
		Ex smoker	47.6% (49/103)	**LDL**	111±49mg/dL
		History of opthalmopathy		**HDL**	42±14mg/dL
		None	25.2% (26/103)	**INR**	1±0.3
		Mild	42.7% (44/103)	**APTT**	32.3±6sec
		Moderate	22.3% (23/103)	**PT**	18.2±5sec
		Severe	9.7% (10/103)	**HbA1C**	8.1±1.2%
				Negative ulcer cultures	63% (65/103)

Table 1. Social-demographics, past-medical history details and blood test results of each patient.

BMI: body mass index; DM: diabetes mellitus; PAD: peripheral artery disease; CAD: coronary artery disease; HT: hypertension; AF: atrial fibrillation; ABI: ankle brachial index; DSA: digital subtraction angiography; CTA: computed tomography angiography; CRD: chronic renal disease; HL: hyperlipidemia; COPD: chronic obstructive pulmonary disease; CVD: cerebrovascular disease; Hb: hemoglobin; WBC: white blood cells; Neu: neutrophils; PLT: platelets; MPV: mean platelet volume; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; Cr: creatinine; Ur: Urea; Na: sodium; K: potassium; ALT: alanine transaminase; AST: aspartate transaminase; CK: creatine kinase; LDH: lactate dehydrogenase; Chol: cholesterol; Trig: triglycerides; LDL: low-density lipoprotein; HDL: high-density lipoprotein; INR: international normalized ratio; APTT: activated partial thromboplastin time; PT: prothrombin time; HbA1C: hemoglobin A1C; cm: centimeter; kg: kilogram; m: meter; µl: microlitre; fl: femtolitre; mm: millimeter; h: hour; IU: International Units; L: Litre; mmol: millimole; U: units; dL: deciletre; sec: second.

i.

Stage	Grade			
	0	I	II	III
A	0	3	0	0
B	0	28	16	3
C	0	30	10	
D	0	8	4	1

ii.

	Ischemia 0				Ischemia 1				Ischemia 2				Ischemia 3			
W0																
W1	1	14				6	1		2	15	4		2	12		
W2		2	5	2			3			1	2			1	1	
W3				1							1					
	F0	F1	F2	F3	F0	F1	F2	F3	F0	F1	F2	F3	F0	F1	F2	F3

Table 2. i. Patients categorized according to Texas Wound Classification system.[6]

ii. Patients categorized according to Wound Ischemia Foot infection Classification system,[8] (W: wound; F: foot infection).

Self-management				
First examination		**After 12 month of follow up**		
Mean Self-examination per week	1.84	**Mean Self-examination per week**	8.4	p< 0.05
Mean Foot washing per week	3.9	**Mean Foot washing per week**	7.8	p< 0.05
Mean foot hydration per week	0.66	**Mean foot hydration per week**	7	p< 0.05
Cutting nails		**Cutting nails**		
Him/herself	64% (66/103)	Him/herself	11.6% (12/103)	p< 0.05
Other	34% (35/103)	Other	70.9% (73/103)	p< 0.05
Specialist	2% (2/103)	Specialist	17.4% (18/103)	p< 0.05
Sock selection	11.6% (12/103)	**Sock selection**	79.6% (82/103)	p< 0.05
Special anatomical shoes		**Special anatomical shoes**		
No	92.2% (95/103)	No	80% (83/103)	ns
Walking barefoot:		**Walking barefoot:**		
Yes	42.7% (44/103)	Yes	7.6% (8/103)	p< 0.05
Visual analog scales				
Mean VAS ADL	6.8±2.5	**Mean VAS ADL**	4.2±1.2	p< 0.05
Mean VAS INT	6.3±2.2	**Mean VAS INT**	2.8±1.3	p< 0.05

Table 3. Hygiene self-management assessment between the first and the last examination (12 months) of follow up. A 10 cm visual analogue scale for the impact of pain on daily living activities of (VAS-ADL) (0–10) and a 10 cm visual analog scale for the pain intensity (VAS-INT) (0, no pain; 10, unbearable pain. ns: not significant.

		Mean	Std. Deviation	Std. Error Mean	P values
Pair 1	Leisure after 12-month follow up	45,8796	21,04544	2,02510	
	Leisure at 1st examination	29,0741	16,74643	1,61143	,000
Pair 2	Physical health after 12-month follow up	45,3704	19,55944	1,88211	
	Physical health at 1st examination	35,3704	17,23536	1,65847	,000
Pair 3	Daily activities after 12-month follow up	46,4815	21,16092	2,03621	
	Daily activities at 1st examination	35,3704	19,39149	1,86595	,000
Pair 4	Emotions after 12-month follow up	40,4861	21,45539	2,06455	
	Emotions at 1st examination	22,7083	16,58004	1,59542	,000
Pair 5	Treatment after 12-month follow up	45,1968	22,32484	2,14821	
	Treatment at 1st examination	33,1019	18,05081	1,73694	,000

Table 4. Quality of life assessment in all domains at baseline (1st examination) and at 12-month follow up.

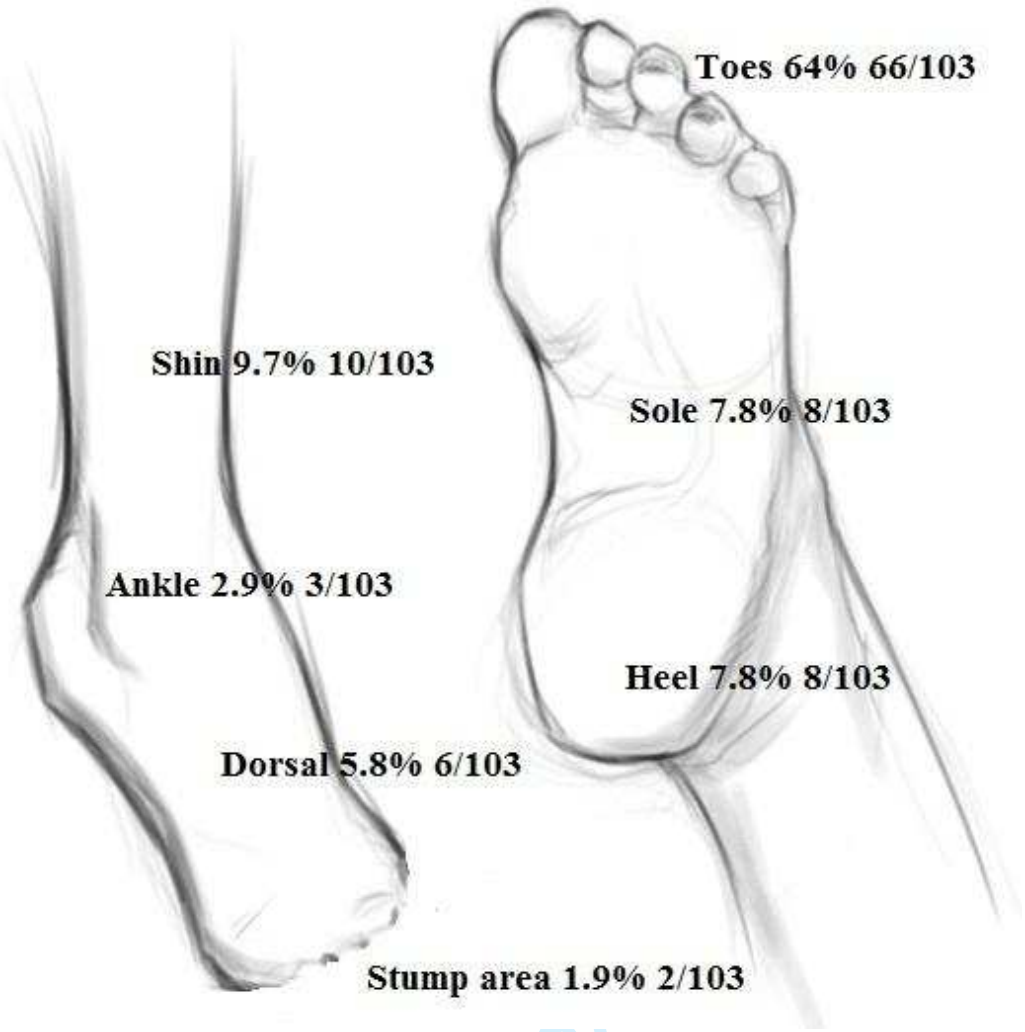

Figure 1. Schematic location of the ulcers.

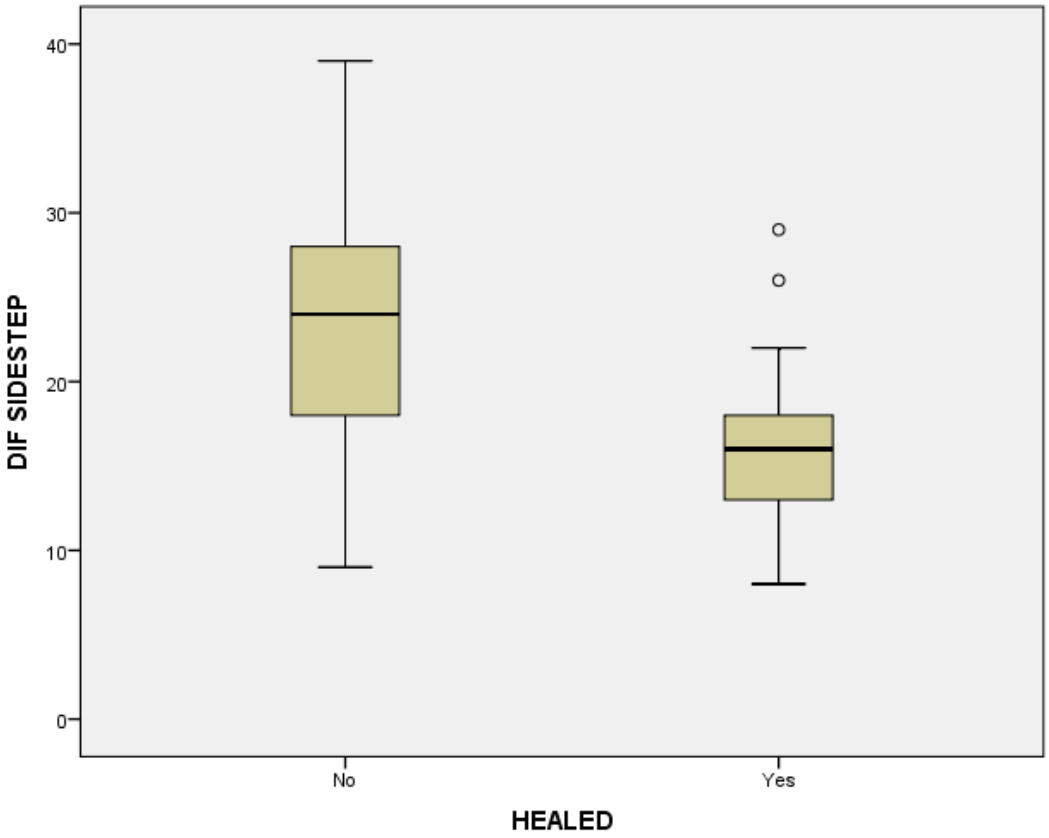

Figure 2. After increase of one DIF score unit, the risk for ulcer non-healing is increased by 15% (95% CI 1.5% – 30%, p=0.028), with mean DIF score 17±2 for ulcer healed patients and 24.5±3 for non-healed patients. (DIF: diabetic foot infection; CI: confidence interval).

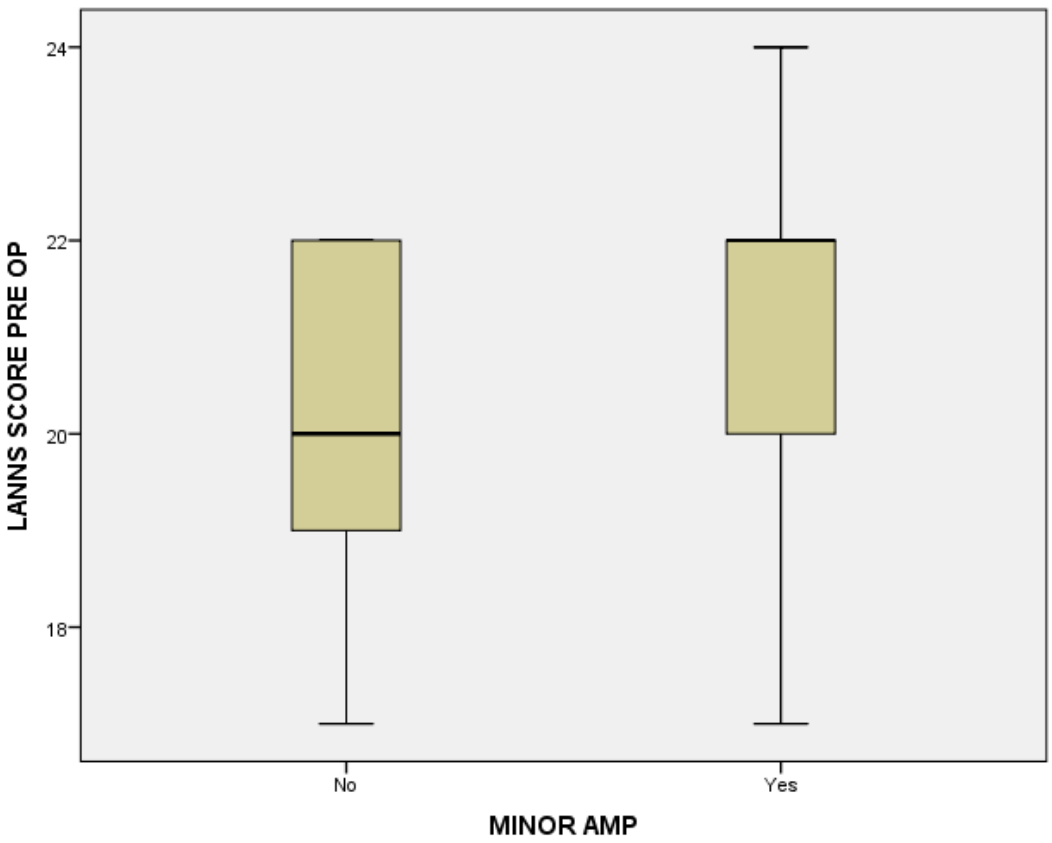

Figure 3. For every increase of one unit of LANSS score the risk for minor amputation is increased by 43% (95% CI 2% – 100%, p=0,040). (LANSS: Leeds Assessment of Neuropathic Symptoms and Signs, CI: confidence interval)