Evaluation of the WIfI classification system in older patients with diabetes

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In January 2014, the Society for Vascular Surgery published its new threatened limb classification system based on Wound extent, degree of Ischemia and foot Infection (WIfI). This classification represents a summary of multiple previously published classifications focused on diabetic foot ulcers and pure ischaemia or infection models. Despite the new system, patient-centred functional outcomes — such as wound healing or maintenance of ambulation — remain incompletely evaluated in this population. By and large, doctors who are using the WIfI classification will report mainly on the risk of amputation and benefit of revascularisation at 1 year, but will not report about patient survival or the probability of ulcers healing.

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There are numerous factors that have an impact on diabetic foot ulcer (DFU) healing, among them critical limb ischaemia (CLI) — a term that was not intended to include patients with diabetic foot wounds and neuropathy. The Society for Vascular Surgery, therefore, created a new classification system for threatened lower extremities in which the severity of ulceration and severity of limb ischaemia are both graded. They also added a grade or classification scheme for infection.

The need to reconsider how the threatened limb is classified is clear. Ischaemia, while of fundamental importance, is but one component among a triad of major factors that place a limb at risk for amputation. The proposed Society for Vascular Surgery Lower Extremity Threatened Limb Classification System is based on grading each of the three major factors: Wound extent, degree of Ischaemia, and foot Infection, or WIfI (Mills et al, 2014). The implementation of this classification system is intended to permit more meaningful analysis of outcomes for various forms of therapy in this challenging and complex heterogeneous population.

During the 1990s, most DFUs were considered neuropathic (Armstrong et al, 2011). The Eurodiale Study, which included 1,229 patients presenting with a new DFU between September 2003 and October 2004, found non-plantar ulcers to be most frequent type of ulcers in this group, affecting 52% of participants (Prompers et al, 2008). The study also reported that a high proportion of DFUs were complicated by infection (58%) or peripheral arterial disease (PAD; 49%), with one-third having both infection and PAD. Individuals with the most severe form of foot disease (stage D) were older, had more non-plantar ulcers, greater tissue loss and more serious comorbidities. Patients with PAD plus infection had poor healing rates; moreover, they suffered from higher rates of amputation and mortality (Prompers et al, 2007).

Ischaemic and neuroischaemic ulcers have similar healing and mortality results, in contrast to neuropathic ones (Moulik et al, 2003). According to international guidelines (Prompers et al, 2007; International Working Group on the Diabetic Foot [IWGDF], 2015), neuroischaemic and ischaemic diabetic ulcer outcomes are connected to factors related to the wound (the most important being the extent of tissue involvement), the leg (severity of PAD) and patients' comorbidities. Apelqvist et al confirmed the importance of these factors in patients with diabetes and CLI. Revascularisation is the major driver for ulcer healing. Both angioplasty and open vascular surgery increased the probability for primary healing (Apelqvist et al, 2011).

Despite this, data about the natural history of the disease are scarce. In a study of 602 patients with DFUs who had severe arterial disease (CLI) who were not revascularised, 50% of patients healed primarily with wound care or with minor amputation; 17% healed, but after major amputation; and 33% died with limbs intact, but with unhealed wounds (Elgzyri et al, 2013). The authors aimed to evaluate the capacity of the WIfI scoring system to predict the risk of amputation at 1 year in older patients with diabetes and with ischaemic or neuroischaemic ulcers, as well as determine the benefit of revascularisation and wound healing time.

Method

Data on ischaemic and neuroischaemic episodes of active ulcer in diabetic patients were collected between February 2011 and June 2012. Data were retrieved retrospectively and patients were prospectively followed and treated according to a standardised protocol until healing was achieved or until death. Patient consent was obtained through the hospital administration department and was in line with the hospital's requirements for clinical data use.

All lesions were assessed and documented by the first author (MPVO) and her team. All patients with diabetes and a DFU were eligible for inclusion. Patients who had a purely neuropathic lesion with no ischaemic component were excluded. Patients were consecutively recruited, followed and treated by the multidisciplinary team at Cruces University Hospital as inpatients for revascularisation and as outpatients until healing was achieved. Outpatient treatment was carried out in collaboration with primary healthcare and home services.

The core team consisted of a vascular surgeon, podiatrist and a registered nurse educated in ulcer treatment (toe and flow model). Vascular investigation was carried out according to a prescheduled programme. A specially trained podiatrist provided a continuous offloading service. A specialist in infectious disease was available for consultations when required. Vascular interventions were performed in a standardised manner after a specialised clinical session discussion.

Patients were offered the best medical treatment to improve their metabolic control and optimise the treatment of any comorbidities they had. Offloading was offered to all patients, with equipment adjusted to their individual needs. Patients who did not agree to offloading were treated with total contact casts, orthoses and insoles, specially-made shoes, half shoes or wheelchairs and felted pads. Patient compliance was defined as following given prescriptions for medical treatment, using offloading equipment and attending team visits.

Factors evaluated

The amputation risk at 1 year, the benefit of revascularisation and wound healing time (WHT) were evaluated. These factors were calculated retrospectively according to the WIfI staging classification. As the study started before the classification was published, the data were recoded according to WIfI scoring.

Offloading therapy, the complexity of the arterial lesions (TASC II classification) and comorbidities were assessed following the Kaiser Permanente pyramid model, as these factors may play a role beyond WIfI in amputation risk and survival at 1 year. The pyramid identifies three levels of intervention according to patients' complexity so that the intensity of care can be adapted to patients' real needs at each level (NHS Institute for Innovation and Improvement, 2006).

Other factors evaluated were previous amputation, smoking habits, duration of diabetes, previous history of heart disease according to the American Heart Association classification and renal disease.

Ulcer duration and wound healing

The duration of an ulcer was defined as the estimated number of days from the development of the ulcer until healing. When clinical signs of infection were present, treatment with oral and intravenous empirical antibiotics was provided in accordance with the 2015 IWGDF recommendations. The presence of osteomyelitis was diagnosed as an open lesion fulfilling at least three of the following criteria from the IWGDF. A probable diagnosis of bone infection is reasonable if there are positive results in a combination of diagnostic tests, such as: probe-to-bone, serum inflammatory markers [ESR], plain X-ray, magnetic resonance imaging (MRI) or radionuclide scanning (strong; weak) (IWGDF, 2015).

Wound healing was defined as the presence of complete epithelialisation or a reduction in ulceration to a superficial level (<1 cm^2) with good granulation tissue growth. In patients in whom two interventions were needed for healing, the date of the first intervention was taken as time "0" for the measurement of healing time. In patients with two lesions, the worst lesion was considered for measurements.

Data management

At study entry, data were collected within a Doctoral Thesis by the first author (MPVO). Patient characteristics, comorbidities, duration of the lesion, ulcer characteristics and management data were recorded continuously during follow-up visits using standardised case record forms. These forms were computerised

Table 1. Characteristics of participants (n=100).

Average age	70.0 years
Male	73.8%
Average HbA_{1c}	62.8 mmol/mol (7.9%)
Comorbidities:	
■ Hypertension	82%
■ Coronary artery disease	53%
■ Chronic kidney disease	38%
On dialysis	6.0%

Table 2. Major amputation at 1 year for various levels of risk (n=124 ulcers).

WIfI amputation risk at 1 year	Major amputation at 1 year		
	No (%)	Yes (%)	Total
Stage 1: very low	5 (100.0)	0 (0.0)	5
Stage 2: low	12 (100.0)	0 (0.0)	12
Stage 3: moderate	30 (88.2)	4 (11.8)	34
Stage 4: high	59 (80.0)	14 (19.2)	73
Total	106 (85.5)	18 (14.5)	124

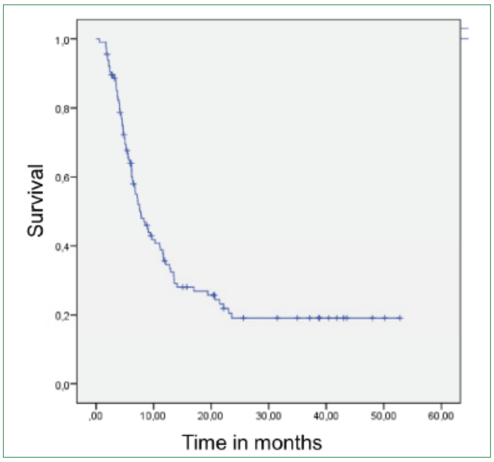

Figure 1. Median time to ulcer healing.

into a Microsoft Excel database and transformed into files. Analysis was carried out using SPSS version 22.0 program.

Results

There were 122 patients with 151 episodes of DFU during the period of the study. Of these, 22 patients had 27 episodes of purely neuropathic ulcers, and were excluded from the study. Data were therefore collected on 124 ischaemic and neuroischaemic episodes of active ulcer in 100 patients with diabetes between February 2011 and June 2012. The dates of the initial lesions were unknown in nine instances. Seven of the 100 patients were lost to follow up.

The baseline characteristics of participants are given in *Table 1*. Their mean age was 70 years and almost three-quarters were men. All participants had diabetes and CLI. Mean HbA_{1c} was 62.8 mmol/mol (7.9%) (standard deviation: 8.6 mmol/mol [1.7%]). There was a high prevalence of comorbidities. Fifty-one per cent was in the Kaiser Permanente highest risk zone.

Of the 124 DFUs, 18 led to major amputation *[Table 2]*. Fourteen (78%) were classified as WIfI stage 4. The remaining four were stage 3. In our study, 72.6% of patients were revascularised; therefore, WIfI had a sensitivity of 77.8% (95% confidence interval [CI], 54.8–91.0) and specificity of 44.3% (95% CI 35.2–53.8) for major amputation. The positive likelihood ratio (LR+) was 1.40 (95% CI 1.04–1.89) and negative likelihood ratio (LR–) was 0.50 (95% CI 0.20-1.23). Patients classified as WIfI stages 1–3 had double the chance of limb salvage as stage 4 patients in LR–. The analysis of the area under the ROC curve, based on the effectiveness of the WIfI scale at predicting amputation risk, was 0.61 (95% CI, 0.47–0.74). All patients who underwent a major amputation had been classified by the WIfI scale as likely to gain high benefits from revascularisation (LR+ 2.08 [95% CI, 1.39–3.13]; LR– 0.00). The median time to ulcer healing was 7.65 months (230 days; 95% CI, 5.72–9.59) *[Figure 1]*.

Previous history of amputation influenced WHT. In this group of patients, the median WHT was 13.4 months. In patients with previous minor amputation, WHT was 15.7 months, and in those with a major amputation it was 34.5 months (CI 95%, 23,50–45.55, P=0.006) *[Figure 2]*.

TASC II classification was another significant factor affecting ulcer healing. The greater the arterial lesion complexity, the worse the outcome. Thus, the average WHT for TASC A lesions was 3.8 months, for TASC B was 4.3 months, for TASC C was 7.2 months and for TASC D was 10.2 months (P=0.005) *[Figure 3]*. The TASC II and WIfI classifications predicted similar wound healing trajectories *[Figure 4]*.

An important positive factor for healing was podiatric treatment at discharge. Sixty per cent of patients complied with podiatric treatment. Patients receiving podiatric therapy took a median of 7.5 months for complete healing compared to 12.1 months for those who had received no podiatric treatment (P=0.012). Podiatric therapy increased the likelihood of healing by 1.8 times.

No statistical assessment of the impact of infection on WHT was possible due to the fact that none of the patients with wounds with

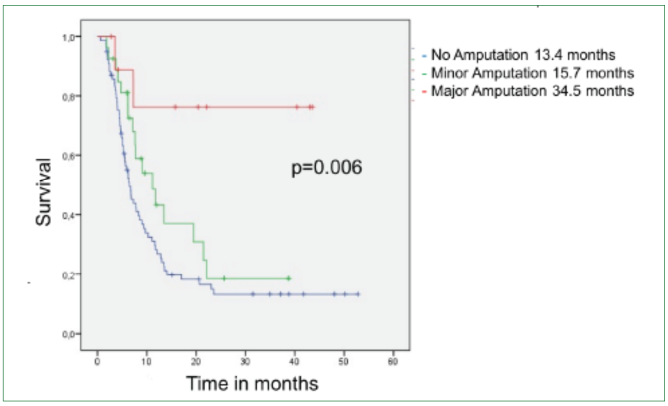

Figure 2. Effect of previous amputation on wound healing time.

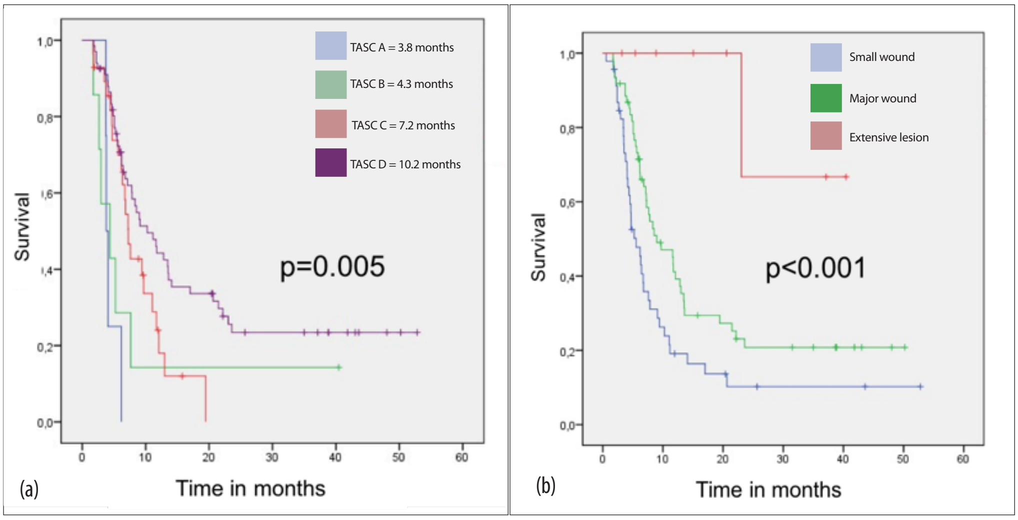

Figure 4. Predicted wound healing trajectories for the TASC II (a) and WIfI classification systems.

extensive infection achieved healing. When we recoded data using a binary model, the average healing time was 6.3 months for no infection or mild infection *versus* 9 months for moderate or extensive infection (*P*=0.094).

Patients classified as likely to receive the least benefit from revascularisation on the WIfI scale had wounds that closed in a mean time of 4 months. Patients expected to get medium benefits from revascularisation healed in 6.7 months and those predicted to benefit the most healed in 7.8 months (*P*=0.015).

Univariate analysis of TASC II classification for the participants demonstrated that the complexity of the lesions had an impact on the probability of healing. Patients classed as TASC A were 6.4 times as likely to heal as individuals classified as TASC D.

Other factors that impacted healing were ulcer size and ankle brachial pressure index (ABPI). Small and superficial ulcers had 14 times better healing than extensive lesions. Patients with ABPI >0.60 were 2.3 times better off than those with ABPI <0.39.

Independent factors involved in WHT were calculated and a Cox regression multivariate was analysis performed *[Table 3]*. We found that the complexity of arterial lesions according to TASC II, extent of the wound according to WIfI and a previous history of amputation were independent risk factors for prolonged WHT.

Table 3. Factors that have an impact on wound healing time.

Factor	*P*-value	Hazard ratio	Inferior (95% CI)	Superior (95% CI)
TASC II (2015)				
A	0.001	6.672*	2.206	20.181
B	<0.001	5.517	2.208	13.783
C	0.028	1.828	1.068	3.126
D (reference)	<0.001			
Lesion size				
Small	0.025	9.959*	1.336	74.252
Medium	0.057	6.985	0.946	51.580
Extensive (reference)	0.040			
Previous amputation				
None	0.010	13.696*	1.868	100.391
Minor	0.044	8.099	1.060	61.874
Major (reference)	0.008			

*Independent risk factor

Discussion

There was a long average WHT in our population, at 7.65 months, in contrast with the average 2.7-month WHT published in an earlier paper validating the WIfI system (Cull et al, 2014). Cull and colleagues did not, however, provide information on participants' risk stage and the duration of the wounds, as time to healing started after revascularisation, thus obviating the ischaemic component prior to intervention. Their figures are, therefore, not comparable to ours, as we coded healing time from the date the lesion was initially identified. A study by Zhan et al (2015) gives a healing time of 94 days in WIfI stage 1, 115 days in stage 2, 163 days in stage 3 and 264 days in stage 4. No data are given for the overall mean period of healing. Nevertheless, our results show longer WHTs, particularly in WIfI stages 3 and 4 *[Table 4]*. The reason for this may lie in the different populations' characteristics. The authors' population is mostly WIfI stage 3 or 4, is older and has more comorbidities. This fact supports the need for homogenisation when comparing results, particularly with regards to participants'

Table 4. Comparison of wound healing times according to WIfI stages.				
WIfI stage	Zhan et al, 2015		Current study	
	Days (%)	Confidence interval (CI)	Days (%)	CI
1	90 (20)	69–119	122 (4.3)	82–162
2	115 (25)	92–139	135 (7.8)	0.03–300
3	163 (25)	105–220	189 (29.5)	142–236

Table 5. Revascularisation impact on wound healing time.		
WIfI stage	Before (days)	After (days)
1	122	–
2	135	122
3	189	201
4	348	235

characteristics. Zhan et al found that healing time shortened after revascularisation from 238 to 94 days in stage 3. They concluded that there was greater revascularisation benefit for WIfI stage 3 individuals. We found similar results for stage 4 patients, who benefitted the most from revascularisation *[Table 5]*.

Multiple studies suggest that patients with an ABPI >0.8 are at lower risk for amputation and unlikely to require revascularisation to achieve healing. In these patients, wound size and infection severity are the major determinants of amputation risk. However, patients with significant wounds and a systolic arterial pressure of <50 mmHg or ankle brachial index of <0.4 are likely to require revascularisation to achieve wound healing and limb salvage (Apelqvist et al, 2011). WIfI grades 3 and 4 were strongly associated with increased amputation risk in our study. We found that correction of perfusion deficit sped up the healing of smaller wounds or was required to heal extensive ones, especially in patients with diabetes or wounds complicated by infection.

It is interesting to emphasise that despite evidence that podiatric therapy is useful for shortening WHT (in our study it reduced WHT from 12 to 7.5 months), only 60% of our patients were compliant. This may be explained by the fact that neuropathic ulcers often require offloading and topical therapy, while revascularisation is often sufficient for ischaemic lesions. We offer ortho-podiatric treatment to patients with ischaemic and neuroischaemic ulcers, as we believe the majority of these lesions in patients with diabetes have a subclinical neuropathic component.

Conclusions

TASC classification, ulcer characteristics and a previous history of amputation are independent factors that affect WHT. The WIfI classification correctly identified the severity of ulcers but was insufficient at identifying ischaemia. Infection did not impact WHT, but was predictive of amputation. The WIfI classification correlated poorly with clinical outcomes regarding risk of amputation during the first year in an older population with diabetes. However, increasing WIfI grades were more predictive of benefit from revascularisation.

More studies are needed in a similar population to verify these results. As the authors of WIfI have often pointed out, the first iteration is like TASC — there is a need for predictive modelling over time to inform and update the design of the scale. WINT

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