

Measurements in Diabetic Foot

Introduction

Complications of diabetes mellitus in the lower limb, generically indicated as Diabetic Foot (DF) are the most frequent cause of limb amputations, such that it has been estimated that a limb is lost every 30 seconds on planet Earth because of diabetes, with a trend towards a four-fold increase in the number of amputations in the next 15 years, due to the pandemic evolution of diabetes.¹⁻²

Diabetic patients bear a risk of lower extremity amputation (LEA) which is 20 times higher than that of the general population and the costs related to this pathology are by far the highest among those related to diabetes mellitus and its complications.³⁻⁴

Although it has been so far considered a local complication, data are emerging in the literature on the important co-morbidity of DF, with a high prevalence of cardiovascular events and pathology, multi-regional macro- and micro-angiopathic involvement, and a significant association with all the aspects of the metabolic syndrome.⁵⁻⁶

For these reasons DF is now considered more properly as a target organ complication of a chronic evolutive disease, and a marker of systemic pathology and severity of disease in both type 1 and type 2 diabetic patients.⁷

Beside its emerging systemic co-morbidity, the local aspects of DF have been well described and understood in their relevance to the evolution of the clinical course of this pathology, and ulceration has maintained a central role in the acute phase of DF: more than 85% of LEAs are preceded by an ulcer, ulcers are the main generator of costs in DF and their management is an essential component of the multi-disciplinary approach to DF therapy, as detailed by the International Consensus Guidelines.⁸⁻¹⁰

The possibility to measure the different aspects of DF and its ulcerative pathology gives to clinicians the chance to both evaluate and weigh up the different components contributing to the genesis and evolution of the cases and to monitor their clinical course as a consequence of the therapeutic interventions.¹¹⁻¹²

In this review a synthetic description of the pathogenetic mechanisms of DF will precede an analysis of the measurements applied to the different clinical presentations along with their relevance and clinical use.

Pathogenesis of the Diabetic Foot

Diabetic foot is actually the consequence of the long-term chronic complications of diabetes affecting the lower limbs: *peripheral neuropathy*, which exposes the foot to an increased risk of developing a chronic foot ulcer inducing deformities which in turn exposes bony prominences to higher pressures and diminishes the sensitivity to external trauma, and *peripheral vascular disease (PVD)* which interferes with the healing process of ulcers, reducing the amount of tissue oxygen and

nutrients, thus lengthening their healing time.^{4,8} Ulcers, especially those with an important ischaemic component, are prone to be colonised by bacteria which can easily complicate the clinical picture with both superficial or deep *infections* and eventually osteomyelitis.¹³

The clustering of these three components, with the external determining contribution of trauma, determines the progression of the pathology from a non-ulcerated condition of a foot at risk, to an acute syndrome characterised by the classic diabetic foot ulcer, followed by a chronic condition in the post-ulcerative phase, which can eventually be associated with a minor amputation.¹⁴

In all cases the identification of three different but inter-related and evolutive conditions is important to better define the measurements that are useful and necessary for that particular aspect of the syndrome.⁴

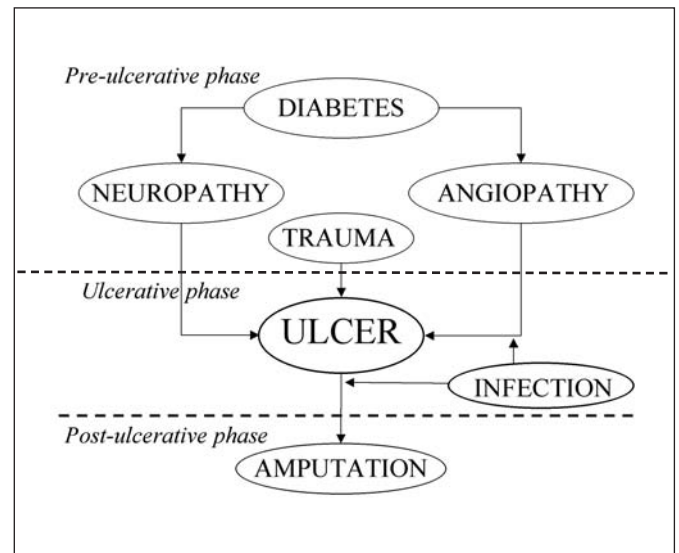


Figure 1. The pathogenesis of DF: from a pre-ulcerative phase, in which the pathogenetic factors are present, without any ulceration; after a variable time interval, an ulcer develops often because of a trivial trauma, leading to an acute ulcerative phase, that transforms a chronic condition into an acute surgical pathology. After healing, eventually with amputation, the patient enters a post-ulcerative phase in which the ulcerative risk is higher than before the first DFU

In the *pre-ulcerative phase* the focus will be on the identification of the risk factors and their quantification, in order to develop a risk profile and to plan the preventive interventions.

In the *ulcerative phase* the emphasis will be on the staging and characterisation of the ulcer and its evolution, to determine the therapeutic strategy and to evaluate the clinical evolution of the conditions.

In the *post-ulcerative phase* follow-up parameters will be selected to identify possible relapses and to adjust the rehabilitative interventions.

In each condition measurement will be performed differently arranged to explore neurological, vascular, bio-mechanical or infection-related aspects, according to the specificity of the actual clinical case.

Measurements in Pre-ulcerative Phase

Up to 15% of diabetic patients will actually develop the diabetic foot syndrome (DFS) at least once in their lifetime, but the prevalence of the component causes of DFS is much higher: peripheral neuropathy has been estimated to be present in about 50% of patients and PVD affects as many as 40% of diabetic patients with long-standing disease.³

The aim of measurements in this phase is to evaluate the risk profile of patients for foot ulceration so that higher risk patients can be appropriately followed and preventive measures and therapies given.

According to the International Consensus Guidelines, the risk profile for diabetic foot ulcers is composed either by neuropathy, presence of deformities and/or peripheral vascular insufficiency and eventually previous amputations or ulcers.¹⁰

Risk Score	Definition	Diagnostic Criteria
0 = Absent	Neuropathy absent	VPT < 25 volt
1 = Medium	Sensory neuropathy	VPT > 25 volt
2 = High	Sensory neuropathy + peripheral vascular disease and/or deformities	VPT > 25 volt + ABPI < 0.9 (or TcpO2 < 60 mmHg) and/or signs and symptoms
3 = Very high	Previous ulcers or amputations	History and clinical signs

Table 1. The integrated score for ulcerative risk in diabetic foot

The neuropathic side of the pathology can be evaluated by determining the sensitivity to a monofilament that applies a force of 10 g/cm² to specific points in the foot (3 to 9 according to different protocols); insensitivity following application of the monofilament identifies a risk condition.¹⁵

The same concept can be used for the determination of vibratory perception with a 128 Hz graded frequency, or with a bio-esthesiometer, an instrument which enables quantifica-

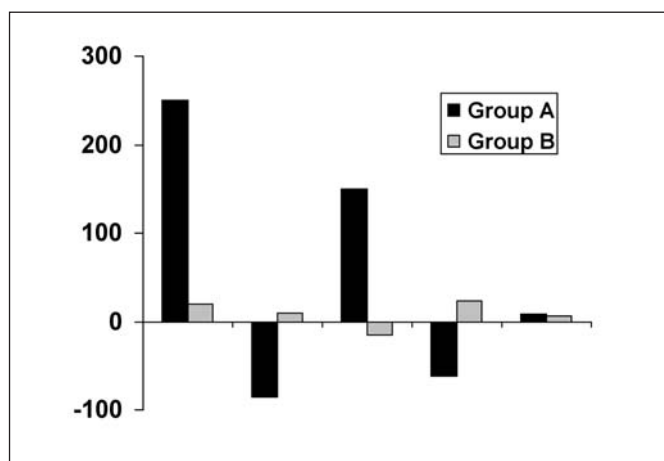


Figure 2. The rate of change from baseline in all the parameters evaluated at the end of the study. We observed a 250% increase in the skin hydration score, and 150% increase in skin moisture, accompanied by an 85% reduction in TEWL and of a 62% reduction in skin hardness. All the differences observed in group A patients, except for skin temperature, were significant, while no significant modification was observed in group B patients

tion of the vibration drive applied to the first toe or to the malleolus of the foot. A threshold of 25 volts identifies the condition of ulcerative risk.¹⁶⁻¹⁷

The vibration perception threshold value (VPT) can also be used to quantify and follow up peripheral neuropathy, in order to evaluate the effects of therapies and to predict the evolution of the pathology. This is possible since the fibres that are responsible for the vibratory component of sensations are the A-δ ones, which are the most myelinated and the fastest ones, as well as the earliest to be involved in the metabolic disturbances typically associated with diabetic neuropathy. In this way a simple, repeatable and non-invasive test is able to evaluate the peripheral nerve damage.¹⁸⁻¹⁹

Recently, a great deal of attention has been paid to the biophysical characteristics of the skin in neuropathic at-risk foot, since they relate to the severity of neuropathy and describe the ability of the skin to act as a barrier to injuries to the neuropathic foot.

It has been demonstrated that neuropathic skin is harder, less elastic, more prone to lose fluids (trans-epidermal water loss - TEWL) and consequently more prone to develop fissures and microlesions which may frequently constitute initial access for infections.²⁰

Moreover, localised hyperkeratosis, measurable with a durometer, has been associated with a very high risk of developing a DFU.²¹

The possibility to measure these variables makes it possible to identify a subject at risk and where necessary to administer moisturizers, as seen in a recent study in which the utilization of nanotechnologies, with the application of microspheres containing a highly hydrating agent coated onto socks worn by the patients at risk, restored all the parameters of skin hydration to normal levels within six weeks as shown in Figure 2.²²

Peripheral vascular disease (PVD) can be assessed clinically, by testing peripheral pulses, but can be better quantified by measuring ankle and toe pressure and calculating the ankle/brachial pressure index (ABPI), which is the ratio between the highest systolic pressure at the ankle and the systolic brachial pressure.⁶

A value >0.9 identifies a normal condition, a value comprised between 0.9 and 0.5 is indicative of the presence of PVD, and below 0.5 a condition of critical limb ischaemia (CLI) is most likely present. On the other hand, an ABPI >1.3 is not reliable, and is frequently related to calcification of the media of arteries (Monkeberg sclerosis), which is actually an indirect sign of autonomic neuropathy.²³

In this case, but also in all other cases, an indirect but precise evaluation of peripheral vascular impairment is the evaluation of the transcutaneous oxygen tension (TcpO2), which evaluates the concentration of oxygen present in a determined

	Normal	PVD	CLI
Ankle pressure (mmHg)	> 100	100 - 50	< 50
Toe pressure (mmHg)	> 50	50 - 30	< 30
ABPI (ratio)	> 0.9*	0.9 - 0.5	< 0.5
TcPO2 (mmHg)	> 60	60 - 40	< 40

Table 2. Ranges of vascular parameters according to the TASC II definitions. * If >1.3 suspect Monkeberg sclerosis

→ area, which is directly dependent on the amount of blood.²⁴
 A TcpO₂ pressure <60 mmHg is indicative of local ischaemia, most likely due to PVD; when values are <40 mmHg, critical ischaemia occurs.²⁵

Table 2 provides a synthesis of the ranges of the vascular measurements in DF related to the severity of PVD according to the second edition of the *Trans-Atlantic Intersociety Consensus guidelines on Peripheral Vascular Disease* (TASC II).²⁶

Deformities of the foot can be clinically evaluated and described as present or not, especially in the forefoot, but even more important is the measurement of the degree of motion of the joints, and to test if limited joint motility condition is present (LJM), which can enhance the exposure of bones and joints to hyper-pressures and consequently the risk of ulceration.²⁷

All these measurements can then be used to compose an integrated score for the ulcerative risk, according to the international guidelines (Table 1), which identifies four different classes, from 0 (= risk absent) to 3 (= very high risk), so that patients in higher risk classes may be followed more closely.¹⁰

Measurements in the Ulcerative Phase

The presence of an acute lesion transforms the foot at risk into an acute clinical emergency, with a potentially very poor outcome; in this phase the evaluation of the condition of the ulcer is the main objective for the clinician, since on this evaluation is based the further management of the patient. Staging of the lesion, evaluation of the presence of infection and of eventual involvement of bones in the lesion are the cornerstones of this process.

The staging of the lesion is the first step of this complex evaluation: the Texas University Staging System (TUSS) is a novel staging scale specifically developed to assess and grade diabetic foot ulcers (Table 3).

It is conceived to give increasing figures from 0 (= no lesions) to III (= lesion penetrating to bone or joint) according to the progressive involvement of deeper structures in the ulcer. A letter is then associated to form a bidimensional score: A is when neither ischaemia nor infection is present, B is for infection, C is for ischaemia, while D indicates that both infection and ischaemia are present.²⁸

To stage the lesion according to such a system is useful not only for the sake of diagnosis, but also for prognostic purposes: it has been demonstrated how poor scores are associated with poor prognosis.

The area of the lesion provides very important information for the clinician, especially its variation over time: it has been demonstrated how a reduction in the area of the lesion in the first week of treatment is a predictor of healing (or non-healing) in DFU.^{11,29}

There are various methods which may be used to assess ulcer area, from the simple measurement of the longest diameter multiplied by the longer orthogonal diameter, which pro-

vides a rough estimation of the real dimension of the lesions, to the very sophisticated and costly technology which allows a 3D reconstruction of the whole lesions with computer-assisted ultrasound equipment.

A good compromise between accuracy and cost is represented by the Visitrak® pad (Smith & Nephew, Hull, UK), an electronic table on which the area of the lesion is automatically calculated when a polyurethane sheet previously applied to the ulcer for designing its margin is applied and the margins are

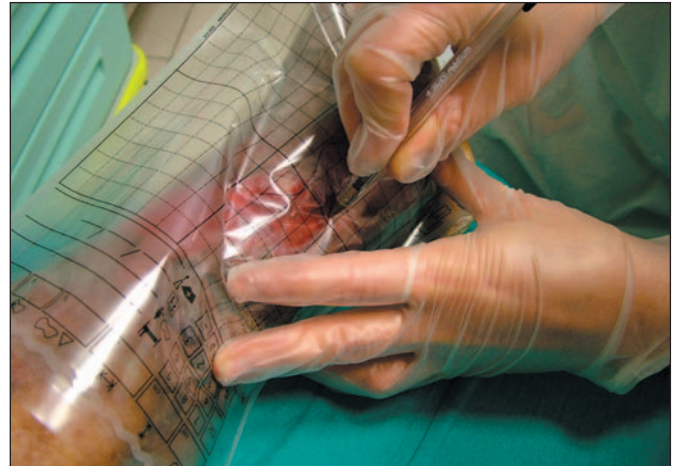


Figure 3a. Measuring the area of the ulcer: a bi-layered polyurethane sheet is placed on the lesion and the margins are traced with a dermographic pen on the gridded outer layer

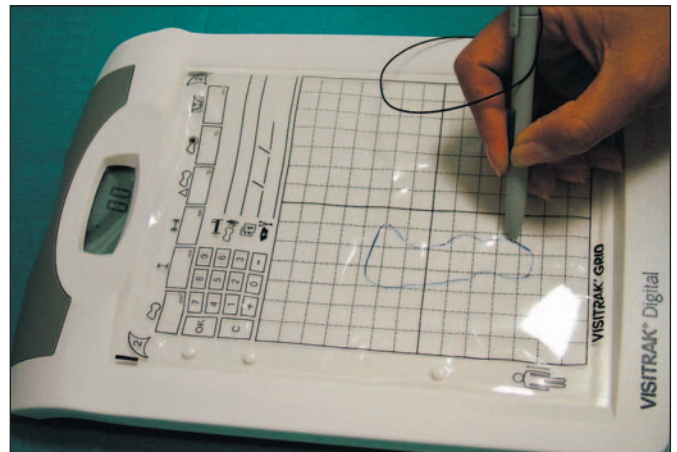


Figure 3b. Measuring the area of the ulcer: the gridded outer layer is then placed on the graphic table and the margins of the lesions are traced with the electronic pen. The area in cm² will be automatically calculated by the Visitrak® device

impressed on the table (Figure 3).

To assess the depth of the lesion, a simple clinical exploration is sufficient in the vast majority of cases, while in a minority of ulcers it may be useful to adopt more sophisticated diag-

	0	I	II	III
A	No open lesion	Superficial ulcer	Ulcer deep to fascia, tendon or joint	Ulcer penetrating joint or bone
B	+ Infection	+ Infection	+ Infection	+ Infection
C	+ Ischemia	+ Ischemia	+ Ischemia	+ Ischemia
D	+ Ischemia and infection	+ Ischemia and infection	+ Ischemia and infection	+ Ischemia and infection

Table 3. The Texas University Staging System (TUSS) for diabetic foot ulcers

nostic instruments like MR in the case of suspected involvement of deeper structures not reachable by probing.³⁰ MRI is important when bones are involved in the lesion, to assess not only their morphological abnormalities, but also their integrity from a functional point of view. MR is able to distinguish, when correctly used, a vital bone from a dead one, and an infected bone from a non-infected one.³¹

Where infection is present, evaluation is mainly clinical, based on the evaluation of local signs such as oedema, redness, secretion, pain, odour, so that quantification is a difficult issue. Nevertheless certain manifestations, especially the extension of the infection may be drawn from the area of peri-lesional cellulitis which, where it is wider than 2 cm, indicate a moderate/severe infection from a mild one.³²

This is relevant not only for correctly diagnosing the condition with which we are faced, but also to prompt an adequately aggressive antimicrobial therapy, comprising, if necessary, hospital admission, surgical debridement and intravenous antibiotics.

Quantitative sampling of the lesion for culture, both by aspiration of the exudate or by biopsies, is another important measurement that may help in ascertaining the nature and severity of infections in DFU: the numbers of CFU (colony forming units) per gram of tissue or exudate is correlated to the severity of infection and, as in the case of ulcer area, may represent a marker for the evolution of the lesions, if analysed longitudinally.³³

Biopsies can also be used to evaluate, with a semi-quantitative score, the histology of ulceration, so as to determine with a high degree of precision the phase of evolution of the healing process, both in basal condition and after a therapeutic intervention.³⁴

In a recent study, histological samples obtained from neuropathic foot ulcers were able to discriminate those in which signs of chronic inflammation were present from those in which the healing process was evolving toward healing, as detailed in Figure 4.

In Table 4 the results of a semi-quantitative analysis performed in histological samples obtained from neuropathic ulcers before (Group A) and after (Group B) offloading are reported: in Group B all the indexes of chronic inflammation were significantly reduced compared with Group A, while there was a sig-

	Group A	Group B	P*
Hyperkeratosis	2.8±0.4	1.8±0.6	0.0018
Fibrosis	2.8±0.4	1.8±0.9	0.0063
Cutaneous Annexes	0.8±0.6	1.9±0.6	0.0018
Capillaries	0.5±0.4	2.5±0.8	0.0003
Inflammation	3±0	1.1±0.3	0.0001
Cellular Debris	2.8±0.6	1.7±1.3	0.0233
Granulating Tissue	0.2±0.4	2.8±0.4	0.0001

Table 4. Semi-quantitative analysis of histological features of neuropathic ulcers before (Group A) and after (Group B) offloading. *Mann - Whitney U; z corrected for ties

nificant increase in the indexes of tissue repair.³⁴

Measurements in Post-ulcerative Phase

After a DFU the diabetic patient with lower limb complica-

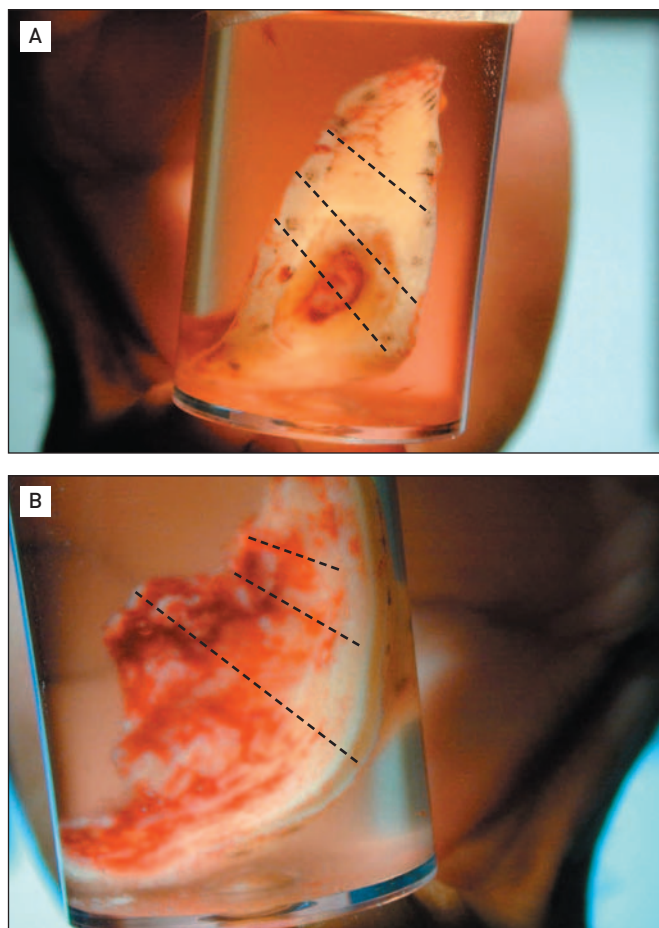


Figure 4. Plantar ulcer after ulcerectomy with the lines for histological sections in plantar (a) and sagittal (b) plans

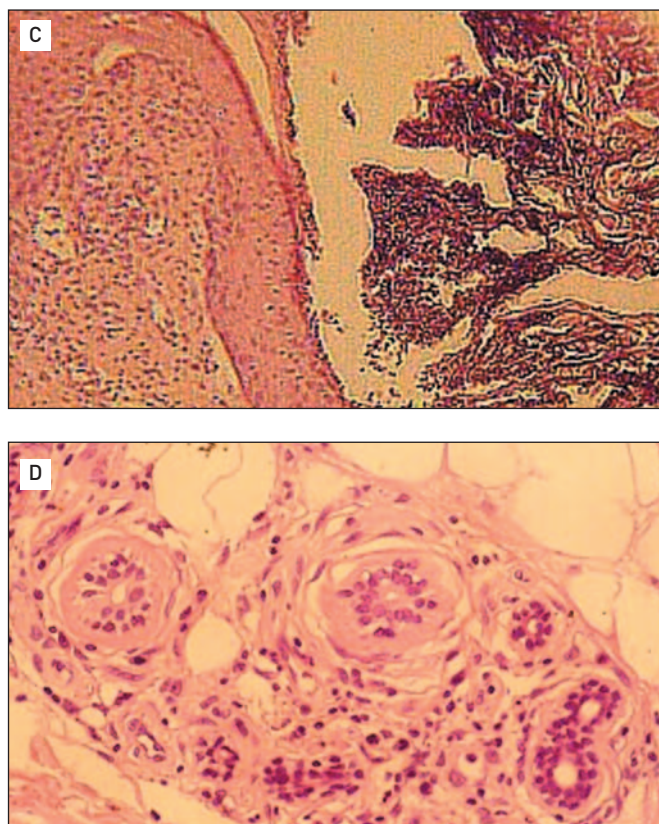


Figure 4. Histology of a DFU in chronic inflammatory (c) and in reparatory (d) phases

→ tions is exposed to recurrences with a probability which is 20 times higher compared with the initial lesion, and this is even more likely if a minor amputation was performed as outcome of the first acute episode.³⁵

In this phase, the emphasis is the secondary prevention, and biomechanical parameters are the most relevant to measure and to reduce the risk of another DFU.

Although it has not been demonstrated that there is a threshold for foot pressure to prevent the development of a DFU, the relation between high peak pressures and the occurrence of a lesion is very well known, and it relates pressure, time of application and area of application in an equation [$W = P \times T/S$] in which the higher the pressure (P) and time of application (T), and the smaller the area of application of pressure (S), the higher the work generated (W) and the probability of developing a recurrence.³⁶

Any localised hyperpressure in the foot has in this model to be considered as a probable area for a future ulcer, irrespective of its absolute intensity.³⁷

To determine the pressures and their areas of applications, there are different methods, from podobarographic maths, simple sheets that register the pressure by the intensity with which the print of the foot transfers the ink onto the paper, to the more sophisticated pobarographic, computer-assisted platforms and insoles, in which the pressures and times of application can be recorded dynamically under any conditions.

Since the purpose of these measurements is to serve as a guide to build insoles and shoes to protect the foot from future DFU, and since it is not the absolute value of the pressure, but its concentration in space and over time that matters, the simple methods, when correctly applied, equal the more complex ones.

Also, foot temperature may be a useful measurement to perform in a preventive strategy: it has been demonstrated that when a new DFU is likely to develop, it is frequently preceded by an increase in foot temperature in the area at risk. According to a new strategy, infrared thermometers have been given to patients at high risk to monitor regularly their foot temperature in a preventive model.³⁸⁻³⁹

The last issue in post-ulcerative DF is the foot with minor amputations: in such cases, especially when toes are concerned, deformities follow the minor amputation performed for the first DFU. It has been demonstrated by the Eurodiale study, a multicentre prospective trial which prospectively evaluated more than 1200 patients coming from 14 highly specialised centres in 10 different European countries, that toe ulcers are the most frequent in DF, so that the recurrences in these patients are the most frequent as well.⁶

These deformities increase the ulcerative risk in the nearby areas of the foot and constitute a variable to consider when we manage post-ulcerative DF.

Measuring the angles of the toes both on the sagittal and on the longitudinal plans is very useful to assess whether the toes are deforming or not: any variation $>5^\circ$ from the previous control should be registered and corrected with silicone orthosis.⁴⁰

The possibility of measuring different aspects of DF is the cornerstone of modern rational approaches to the diagnosis and care of this complex pathology, and should be integrated in the clinical practice of any centre committed to care of DF.

Since the measurements are related to the different phases in the evolution of DF, clinicians may be able to monitor all the variables which are relevant to the monitoring of the evolution of the pathology towards complete healing and to avoid the frequent recurrences. ■

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