Various systems have been developed to classify diabetic foot ulcers for daily practice. Moreover, for research purposes no system has found universal acceptance, which clearly hampered communication in the field of research. In 2003 the IWDGF introduced, as a progress report, its classification system (PEDIS) for research purposes, which is described in this chapter. This system was developed by experts involved in clinical research from all over the world and was based on the experience gained from using earlier classification systems. After its introduction, the IWDGF classification system for research purposes is being used in a growing number of studies, underscoring its applicability in clinical research. Moreover, the system, in particular the part on infection, was also used by Infectious Diseases Society of America (IDSA) for the development of a classification system for diabetic foot infections.

This IWDGF-IDSA infection grading system was validated in a recent longitudinal study, using amputation and lower extremity-related hospitalization as end-points.

**Aims of the ulcer research classification system**

The aims of the research classification system are to enable the categorization of different populations of diabetic patients with a foot ulcer for the purposes of research, at a certain time point, using terms which are unambiguous and applicable world-wide. Such a classification system, according to established criteria, should facilitate communication and enable the comparison of the results of different research projects. It needs to be reproducible, reliable and robust. The research system does not primarily aim to influence clinical management or to predict the outcome of individual foot ulcers and nor is it designed as a monitor of the healing process. These items can be covered by a clinical classification system or could be included as part of specific research projects.

**Definitions and categorisation for the ulcer research classification**

The present research classification system was particularly developed to facilitate communication in the field of research. The system should help to correctly interpret data in research projects; the system should include the major dimensions affecting pathogenesis, management and outcome of a diabetic foot ulcer. It was not the aim to develop a classification system that can be used to predict the outcome of an individual patient or that can act as a guide for daily management. The research system should categorise and define patients with the use of relevant clinical items in such a way that intra- and interobserver variability is low (good reproducibility). Strict criteria defining categories of patients should be given, to reduce the chance of a patient being misclassified.

The consequence of such a rather "rigid" system is that some patients cannot be classified. To optimise comparison between clinical trials it is preferable that some patients cannot be included when they do not fit into the pre-specified categories, rather than that patients are included when they should have been excluded. The latter situation would clearly hamper the generalisation of the results obtained. The consequence is also that, as far as possible, objective, reproducible techniques should be used, to reduce variability.

A concern is that if objective, reproducible techniques are to be used, these techniques can...
become too complex or expensive. The consequence would be that only patients attending highly specialised foot clinics could be classified. Therefore, in several categories of the current system, a compromise was made between the ideal world and daily life, and a minimal set of criteria was given. Depending upon the aim of an individual research project, additional criteria can, and in some cases should be added to the current system to improve correct categorisation (inclusion and exclusion criteria) of the different subcategories.

The current system is primarily developed to characterise patients participating at a certain time point in a research project, usually during the inclusion phase of a project and it should be the basis for the inclusion and exclusion criteria. Therefore, temporal aspects are not included in the current system. However, wounds clearly change in time and complications can develop. When, for instance, the chronobiology of wounds is studied an extra category on wound characteristics can be added.

The definition of an ulcer

A diabetic foot ulcer is defined in the research system as a “full-thickness” lesion of the skin, i.e. a wound penetrating through the dermis; lesions such as blisters or skin mycosis are not included in this system. The term ulcer can be ambiguous in this context. In medicine a skin ulcer is generally defined as a non-healing or poorly healing wound. Information on the duration of the ulcer is essential to define non-healing. Unfortunately, this temporal information is frequently missing in patients with a diabetic foot ulcer: due to loss of sensation and impaired vision the duration is frequently not known. A foot ulcer is defined in the current system, according to the International Consensus on the Diabetic Foot, as a full thickness wounds below the ankle in a diabetic patient, irrespective of duration. Skin necrosis and gangrene are also included in the current system as ulcers. Gangrene was defined in the International Consensus on the Diabetic Foot as a continuous necrosis of the skin and the underlying structures (muscle, tendon, joint or bone).

The categories and grades

On the basis of the scientific literature and expert opinion, five categories were identified, which were considered the most relevant items for research projects in diabetic foot ulcers:

<table>
<thead>
<tr>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perfusion</td>
</tr>
<tr>
<td>Extent/size</td>
</tr>
<tr>
<td>Depth/ tissue loss</td>
</tr>
<tr>
<td>Infection</td>
</tr>
<tr>
<td>Sensation</td>
</tr>
</tbody>
</table>

Loss of protective sensation and impaired tissue perfusion caused by atherosclerotic peripheral arterial disease (PAD) are two basic mechanisms in the pathway to ulceration. They both affect wound management and, in addition, PAD can have a major impact on the outcome. Also, infection and depth have a major effect on management and outcome, and size is particular relevant for the time to heal and wound management.

For each category a grading system is provided, and this grading system should describe the severity within each category. As the system has been developed for primarily clinical research, the criteria for each category are based upon objective techniques that can be part of the up-to-date management of patients with a foot ulcer, as described in The International Consensus on the Diabetic Foot. How each category is graded depends upon the characteristics of that category and the current evidence base. A system which for instance has three grades, such as none - a little - a lot, seems very attractive. Moreover, if all categories are graded identically, it could render the system more easy to use. However, at present the disadvantages of such a symmetrical system seem greater than the advantages. The evidence base (and consensus) to subdivide all categories in three strict grades is lacking. For instance, in the current system there is no grading for size, it is reported in square centimetres and sensation is defined as loss or no loss of protective sensation. The system does not include a grade 0 because in many instances it will be impossible to exclude subclinical abnormalities, for example, in neuropathy or PAD.
The backbone of the present system can be used in any country, but resources are clearly absent in some countries to classify patients according to the strict criteria of the current system. When resources are lacking, the system can easily be adapted for local use. However, lack of resources cannot be an excuse for inadequate research.

**Diabetic foot ulcer classification system for research purposes**

**Perfusion**

The classification system for the diabetic foot is designed to be in line with the system for classification of peripheral arterial disease (PAD) as developed by the TransAtlantic interSociety Consensus group (TASC). More specific criteria are used in the present system, as the TASC system is an inclusive clinical system and not an exclusive research system.

<table>
<thead>
<tr>
<th>GRADE 1</th>
<th>No symptoms or signs of PAD in the affected foot, in combination with:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Palpable dorsal pedal and posterior tibial artery or</td>
</tr>
<tr>
<td></td>
<td>• Ankle Brachial Index 0.9 to 1.10 or</td>
</tr>
<tr>
<td></td>
<td>• Toe Brachial Index &gt; 0.6 or</td>
</tr>
<tr>
<td></td>
<td>• Transcutaneous oxygen pressure (TcPo2) &gt; 60 mmHg</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GRADE 2</th>
<th>Symptoms or signs of PAD, but not of critical limb ischemia (CLI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Presence of intermittent claudication*, as defined in the document of the International Consensus on the Diabetic Foot or</td>
</tr>
<tr>
<td></td>
<td>• Ankle Brachial Index &lt; 0.9, but with ankle pressure &gt; 50 mmHg or</td>
</tr>
<tr>
<td></td>
<td>• Toe Brachial Index &lt; 0.6, but systolic toe blood pressure &gt; 30 mmHg or</td>
</tr>
<tr>
<td></td>
<td>• TcPo2 30 - 60 mmHg or</td>
</tr>
<tr>
<td></td>
<td>• Other abnormalities on non-invasive testing, compatible with PAD (but not with CLI).</td>
</tr>
</tbody>
</table>

Note: if tests other than ankle or toe pressure or TcPo2 are performed, they should be specified in each study.

<table>
<thead>
<tr>
<th>GRADE 3</th>
<th>Critical limb ischemia, as defined by:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Systolic ankle blood pressure &lt; 50 mmHg or</td>
</tr>
<tr>
<td></td>
<td>• Systolic toe blood pressure &lt; 30 mmHg or</td>
</tr>
<tr>
<td></td>
<td>• TcPo2 &lt; 30 mmHg</td>
</tr>
</tbody>
</table>

* In case of claudication additional non-invasive assessment should be performed

**Comments**

Physical examination is one of the cornerstone in diagnosing PAD and needs to be performed by a health-care worker with adequate knowledge and skills. Pain at rest is a criterion for critical ischemia in non-diabetic patients with PAD. Pain at rest is not included in the current research system, as it is difficult to differentiate from other causes of pain in the lower extremity in diabetic patients.

In the UKPDS study symptoms of claudication were reported in only 23% of the patients with an
ankle arm index < 0.8, indicating that for each patient with claudication there are three patients with silent PAD. On the basis of the present literature, the presence of both pulses in the foot, in combination with the absence of intermittent claudication, renders significant PAD unlikely. However, palpation of pulses has only a moderate reproducibility and severe ischemia can be present in a minority of diabetic patients with palpable pulses. On the other hand, if one or two pulses are absent, clinically relevant PAD is more likely, but pulses can be absent due to anatomical abnormalities or edema. Therefore, in the absence of one or two palpable pulses, additional objective vascular assessment is necessary to exclude PAD or to further grade PAD, if present.

In non-diabetic patients measurement of the systolic ankle blood pressure with a hand-held Doppler device is the first step in the evaluation of patients with suspected PAD. The ankle/brachial index (ABI) is calculated by dividing this ankle pressure by the Doppler pressure measured in the brachial artery. An ABI < 0.9 confirms haemodynamically significant occlusive disease between the heart and the ankle, which, in most cases lies distal to the renal arteries. Moreover, the ABI can give a rough estimate of the severity of the occlusive disease in non-diabetic subjects. The index is decreased to 0.5 to 0.9 in asymptomatic patients or in patients with claudication, and most of these patients will have single segment occlusions. Values below 0.5 indicate severe multisection disease, and, in (nondiabetic) patients with rest pain the absolute ankle pressure is usually < 40 mmHg.

Unfortunately the usefulness of this technique can be limited in the diabetic patient. Owing to arterial media calcification, the arteries of the lower leg may be less compressible, and incompressible arteries have been observed in up to 30% of diabetic patients. An ABI > 1.10 suggests that the ankle pressure is falsely elevated. Several studies have shown that the ABI or the absolute ankle pressure is a poor predictor of outcome (amputation) in diabetic patients with PAD and/or a foot ulcer. In contrast, the more complex techniques such as systolic toe pressure measurement or measurement of the transcutaneous partial pressure of oxygen (TcPo2) were better predictors of outcome in several studies.

Media arterial calcification seems to be less of a problem when measuring systolic toe pressures. For screening purposes a toe systolic blood pressure index of >0.60 can be interpreted as normal. Toe pressures can predict outcome in diabetic patients with foot ulcers and primary healing of a foot ulcer occurred in most patients with a toe pressure > 30 mmHg. Unfortunately, this measurement also has limitations. Toe arteries can be affected by media calcification, although to a lesser extent than the arteries in the lower leg, resulting in falsely elevated values. In addition, falsely low values can be obtained if the skin temperature of the toe is too low and in these cases the foot must be warmed prior to the investigation. The transcutaneous partial pressure of oxygen (TcPo2) can be measured with a heated oxygen sensitive probe, which is placed on the dorsum of the foot. Subsequently, the skin oxygen tension can be determined, reflecting local microcirculatory blood flow. In healthy subjects, a wide range of values can be observed, but normal values are usually >60 mmHg. Several studies have shown that TcPo2 values can predict healing or amputation in patients with a foot ulcer. An oxygen tension < 30 mmHg suggests critical limb ischemia in a patient with a foot ulcer. However, it should be noted that various systemic factors (such as hypoxia) or local factors (such as edema and inflammation) can affect the measurement, resulting in falsely low values. Given the uncertainties related to the ABI, it is suggested that in studies aiming to exclude patients with clinical relevant vascular disease, toe pressures or TcPo2 should be determined.

**Extent/size**

Wound size (measured in square centimetres) should be determined after debridement, if possible. The outer border of the ulcer should be measured from the intact skin surrounding the ulcer. If wound healing is one of the end-points in a study, tracing of the wound, planimetry or the grid technique should be used for sequential measurements of the wound area. If, on the other hand, wound size is measured only at the time of recruitment into a study and intact skin is the primary end-point, the surface area can also be estimated by multiplying the largest diameter by the second largest diameter measured perpendicular to the first diameter. However, this technique
is clearly less precise. The frequency distribution of the size of the ulcers should be reported in each study as quartiles.

**Depth/tissue loss**

Depth is difficult to determine and relative, an ulcer which is only a few millimeters deep on a toe can penetrate into bone or a joint, but, in other regions, ulcers can be several centimeters deep without involvement of deeper structures. Therefore, ulcers are divided into lesions confined to the skin and those deeper than the skin. Even if an ulcer does not seem to penetrate below the skin, clinical infection in subcutaneous tissues (e.g., an abscess or osteomyelitis) means it is a "deep" ulcer. The extent of tissue loss should be evaluated after initial debridement, but this should be performed judiciously when critical limb ischemia (Grade 3) is suspected.

**GRADE 1**
Superficial full thickness ulcer, not penetrating any structure deeper than the dermis

**GRADE 2**
Deep ulcer, penetrating below the dermis to subcutaneous structures, involving fascia, muscle, or tendon

**GRADE 3**
All subsequent layers of the foot involved, including bone and/or joint (exposed bone, probing to bone)

**Infection**

Infection of a diabetic foot ulcer is defined as invasion and multiplication of microorganisms in body tissues associated with tissue destruction or a host inflammatory response. Infection is defined clinically, by the symptoms and signs of inflammation as described below, regardless of the results of any wound culture.

Studies on accuracy and validity of different tests for diagnosing infection in diabetic foot disease are scarce. Therefore, the scheme described below is based mainly on expert opinion.

In grading infection, three parameters, in particular, are relevant to clinical management and possibly to outcome: the involvement of skin only, the involvement of deeper structures and the systemic inflammatory response of the patient. In daily practice the term a "limb-threatening" infection is also frequently used. However, this category is very difficult to define and overlaps with the other categories.

**GRADE 1**
No symptoms or signs of infection

**GRADE 2**
Infection involving the skin and the subcutaneous tissue only (without involvement of deeper tissues and without systemic signs as described below). At least 2 of the following items are present:

- local swelling or induration,
- erythema > 0.5 to 2 cm around the ulcer
- local tenderness or pain
- local warmth
- purulent discharge (thick, opaque to white or sanguineous secretion)

Other causes of an inflammatory response of the skin should be excluded (e.g., trauma, gout, acute Charcot neuro-osteoarthropathy, fracture, thrombosis, venous stasis)

**GRADE 3**
Erythema > 2 cm plus one of the items described above (swelling, tenderness, warmth, discharge) or

Infection involving structures deeper than skin and subcutaneous tissues such as abscess, osteomyelitis, septic arthritis, fasciitis.
No systemic inflammatory response signs, as described below.

**GRADE 4** Any foot infection with the following signs of a systemic inflammatory response syndrome (SIRS). This response is manifested by two or more of the following conditions:

- Temperature > 38 or < 36°Celsius
- Heart rate > 90 beats/min
- Respiratory rate > 20 breaths/min
- PaCO2 < 32 mmHg
- White blood cell count > 12,000 or < 4,000/cu mm
- 10% immature (band) forms

**Comments**

The presence of ischemia has a large effect on the signs and symptoms, the clinical course and the outcome of an infection. The combination of infection and ischemia had the poorest prognosis in prospective studies.

Unfortunately, there is, as yet no consensus on criteria for diagnosing osteomyelitis as part of the International Ulcer Research Classification.

The following procedures may be useful in evaluating the presence of an osteomyelitis:

- Plain X-ray abnormalities are relatively insensitive and nonspecific, but repeated X-rays over several weeks can be highly suggestive of, or largely exclude, osteomyelitis.
- Probing to bone in the presence of an infected foot ulcer, based on limited data, appears to have intermediate sensitivity and specificity. The predictive value of the test varies directly with the prevalence of osteomyelitis in the population and no information has been published on intra- and inter-observer variability.
- Nuclear medicine scanning has good sensitivity, but low to moderate specificity depending on the type of scan; leucocyte and immunoglobulin scans appear to be more specific than bone scans.
- MRI has shown good sensitivity and specificity in many studies, but false positive findings can occur, and quality depends on the expertise of the technicians and radiologists.
- Bone biopsy with histology and culture is usually viewed as the gold standard, but published literature in diabetic foot disease is sparse. Moreover, inaccurate results occur when patients are receiving antibiotics, when incorrect techniques are used or due to sampling error.

**Sensation**

The system categorises patients as having present or absent protective sensation in the affected foot. The system does not categorise patients as having (diabetic) polyneuropathy, and additional information is needed for this diagnosis. Moreover, it does not provide information on the cause of the loss of protective sensation, nor is the severity of the sensory loss graded. Both pressure and vibration sensation should be determined in each patient.
GRADE 1  No loss of protective sensation on the affected foot detected, defined as the presence of sensory modalities described below

GRADE 2  Loss of protective sensation on the affected foot is defined as the absence of perception of the one of the following tests in the affected foot:

- Absent pressure sensation, determined with a 10 gram Monofilament, on 2 out of 3 sites on the plantar side of the foot, as described in the International Consensus on the Diabetic Foot
- Absent vibration sensation, (determined with a 128 Hz tuning fork) or vibration threshold > 25 V, (using semi-quantitative techniques), both tested on the hallux.

Comments

Loss of protective sensation plays a crucial role in the pathogenesis of most diabetic foot ulcers treated in diabetic foot clinics. However, in diabetic patients with a foot ulcer treated in these clinics, protective sensation can be present, albeit in a minority of patients. Moreover, it is likely that loss of protective sensation is less prevalent in diabetic patients with foot problems treated in departments of vascular surgery. Therefore, loss of protective sensation is included in the present classification scheme. The testing of light touch and testing of blunt/sharp sensation are not recommended due to lack of scientific evidence.

Further reading

Deep foot ulcer (depth: grade 4) with osteomyelitis (infection: grade 3) caused by local administration of steroids treating a plantar tendonitis.

Insensitive foot: foreign body - a needle - identified through X-ray.

Infected foot ulcer with systemic manifestations (grade 4) associated with ischemia of the forefoot with high probability for major amputation.