Endocrine (2012) 41:384–397
DOI 10.1007/s12020-012-9619-x

REVIEW

Diagnostics and treatment of the diabetic foot

Jan Apelqvist

Received: 11 November 2011 / Accepted: 27 January 2012 / Published online: 25 February 2012

Abstract Every 30 s, a lower limb is amputated due to diabetes. Of all amputations in diabetic patients 85% are preceded by a foot ulcer which subsequently deteriorates to a severe infection or gangrene. There is a complexity of factors related to healing of foot ulcers including strategies for treatment of decreased perfusion, oedema, pain, infection, metabolic disturbances, malnutrition, non-weight bearing, wound treatment, foot surgery, and management of intercurrent disease. Patients with diabetic foot ulcer and decreased perfusion do often not have rest pain or claudication and as a consequence non-invasive vascular testing is recommended for early recognition of ulcers in need of revascularisation to achieve healing. A diabetic foot infection is a potentially limb-threatening condition. Infection is diagnosed by the presence or increased rate of signs inflammation. Often these signs are less marked than expected. Imaging studies can diagnose or better define deep, soft tissue purulent collections and are frequently needed to detect pathological findings in bone. The initial antimicrobial treatment as well as duration of treatment is empiric. There is a substantial delay in wound healing in diabetic foot ulcer which has been related to various abnormalities. Several new treatments related to these abnormalities have been explored in wound healing with various successes. An essential part of the strategy to achieve healing is an effective offloading. Many interventions with advanced wound management have failed due to not recognizing the need for effective offloading. A multidisciplinary approach to wounds and foot ulcer has been successfully implemented in different centres with a substantial decrease in amputation rate.

Keywords Diabetic foot · Foot ulcer · Infection · Ischemia · Treatment · Revascularisation

J. Apelqvist (✉)
Department of Endocrinology, University Hospital of Skåne (SUS), 205 02 Malmö, Sweden
e-mail: Jan.apelqvist@skane.se

J. Apelqvist
Division for Clinical Sciences, University of Lund, Lund, Sweden

Background

The diabetic foot can be defined as infection, ulceration and/or destruction of deep tissues associated with neurological abnormalities and various degree of peripheral vascular disease in the lower limb [1–3]. Foot complications in diabetes present a particularly troubling picture and it has been claimed that every 30 s, a lower limb is amputated due to diabetes [2]. It is estimated that 50–70% of all lower extremity amputations are related to diabetes [1–3]. Of all amputations in diabetic patients 85% are preceded by a foot ulcer which subsequently deteriorates to a severe infection or gangrene [1–3].

Peripheral neuropathy

The most important factors related to the development of foot ulcers in individuals with diabetes are peripheral neuropathy, minor foot trauma, foot deformity and decreased tissue perfusion [4–10]. A sensory neuropathy is associated with the loss of pain, pressure awareness, temperature sensation and proprioception. Due to the lack of protective sensation the foot is vulnerable to unattended minor injuries caused by excess pressure or mechanical or thermal injury. Thus, acute injury, ill-fitting shoes or walking barefoot can precipitate an ulcer [5, 6, 8, 10].

Motor neuropathy, affecting both the intrinsic foot muscles and leg muscles, alters the biomechanics and gradually foot anatomy due to postural instability and disturbed coordination caused by the lack of proprioceptive feedback from the lower extremities [9].

Foot deformities, limited joint mobility and altered loading of the foot are obvious consequences from these disarrangements. This process leads to excess pressure, skin thickening and callus formation, which again increases the already abnormal loading and, often, subcutaneous haemorrhage and ulcer [7–9]. The neuropathic bone and joint disease, usually affecting mid or hindfoot, sometimes referred to as 'charcot foot' or neuro osteoarthropathy [11, 12] can cause severe deformity and plantar ulceration.

In large cohort studies in Europe neuroischemic or ischemic ulcers accounted for 50–58% of all diabetic foot ulcers admitted to specialist care [13–16]. There are no peripheral artery lesion specific to diabetes but the pattern of arteriosclerosis is different typically affects more distal segments, and is of greater prevalence than in non-diabetic subjects [17].

Although microangiopathy should not be accepted as a primary cause for a diabetic ulcer [18], microvascular dysfunction plays a contributing role of poor ulcer healing in neuroischemic diabetic foot [19, 20].

Initially the term 'small vessel disease' or 'microangiopathy' has been used to describe an obstruction of arterioles in the diabetic foot indicating that the patient was considered unsuitable for revascularisation [18].

However, research has refuted the notion of an arteriolar occlusive lesion associated with diabetes and ascribed infrapopliteal macrovascular disease and microvascular dysfunction as major proponents for impaired perfusion of diabetic foot [18, 20, 21]. The microvascular dysfunction (or 'microangiopathy') is characterized by the presence of arteriovenous shunting, precapillary sphincter malfunction, capillary leakage, venous pooling, hormonal activity in the vessel and inflammation in the wall all indicating that decreased perfusion in the diabetic foot is more complex and not only related to peripheral arterial disease [17, 19–21].

Peripheral vascular disease and neuropathy are frequently present in the same patient [13–16]. A possible role of genetic factors in the development of diabetic foot with regard to neuropathy and peripheral artery disease (PAD) has been suggested/discussed [22].

An important observation relating to the consequence of peripheral vascular disease is that many diabetic individuals with ischaemia do not have severe rest pain or claudication [1, 3, 13–16]. This is believed to be related to the loss of sensation due to peripheral sensory neuropathy [1].

Diabetic foot ulcers should be managed by a multidisciplinary team, comprising individuals who can deliver all the necessary and wide-ranging skills: medical and surgical, podiatric, nursing and orthotic [1, 3, 10, 23–29]. Using a protocol-driven and multidisciplinary approach will lower the number of people suffering from numerous foot complications of diabetes [2, 3].

The cause and associated systemic factors that impair wound healing need to be treated—hyperglycaemia, cardiovascular disease, peripheral vascular defects, increased incidence of bacterial infections and plantar pressure redistribution (Table 1, Ref [30–36]). The medical management of ulcers includes offloading, treatment on infection (local, cellulitis, osteomyelitis or sepsis), debridement, wound bed preparation and dressings (Table 1). Surgery is often needed for the treatment of infected ulcers and for the revascularisation of the limb [28, 29].

A multidisciplinary approach to wounds and foot ulcer has been successfully implemented in different centres in different countries with various health care delivery systems with a substantial decrease in amputation rate [10, 24–27]. Two comparative studies have shown improved clinical results with multidisciplinary treatment vs standard care in ordinary practise [184, 185]. According to the most optimistic view up to 85% of the amputations may be prevented [10, 24, 26].

Vascular intervention

Why CLI criteria for non-diabetics are not applicable

The need for revascularisation in neuroischemic diabetic foot ulcers has been determined by the presence of claudication and rest pain or extent of tissue loss along the lines of different classifications and recommendations [37–43]. Yet, <25% of diabetic individuals with PAD report intermittent claudication [2, 3, 10, 31], and that in individuals with diabetic foot ulcers rest pain are substantially less frequent than in individuals with ischaemia without diabetes [2, 3, 10, 31]. The obvious consequence has been that in most clinics, centres and countries diabetic individuals come too late to vascular consultation. Indeed, 30–50% of their foot ulcers already have gangrene and therefore these patients often are not considered candidates for revascularisation [2, 10, 14].

To prevent the delay of vascular consultation and revascularisation early non-invasive vascular evaluation is important in identifying patients with poor ulcer healing and high risk for amputation [2, 10, 14, 16, 44–46].

There is a need to introduce and recognize decreased perfusion or impaired circulation as indicator for the need of revascularisation in the diabetic foot to achieve and maintain healing and to avoid or delay a future amputation [2, 3, 10, 14, 16, 28, 45, 47]. That is the rationale behind the recommendation to use non-invasive vascular testing (toe, ankle pressure, TCO2, duplex) to identify patients with foot ulcer with severe vascular disease impairing wound healing [3].

Table 1 Multifactorial management of diabetic foot ulcer

Goal	Investigation/evaluation	Treatment
Improve circulation	Clinical investigation	Percutaneous angiography (PTA)
	Non-invasive vascular testing	Subintimal angioplasty
	Systolic toe/ankle blood pressure	Reconstructive vascular surgery
	Transcutaneous oxygen pressure	Vascular agents
	Duplex (ultrasound)	Remove oedema
	Invasive vascular testing: angiography	Hyperbaric oxygen
	Magnetic resonance imaging	
	CT angiography	
	CO_2 angiograpy	
Treat infection	Superficial/deep infection, osteomyelitis, abscess	Antibiotics oral/parenteral
	ESR, CRP, white blood count, bacterial culture, bone biopsy, X-ray, CT-bone scan, MRI	Incision/drainage
		Resection
		Amputation
Remove odema	Evaluate cause of oedema	External compression therapy
		Intermittent compression (pumps)
		Diuretics
Pain control	Cause/type of pain, pain evaluation protocol/diary	Analgesic agents local/systemic
	Visual analogue scale	Immobilisation/offloading relive anxiety/fear
Improve metabolic control	HbA1c self-monitoring of glucose	Insulin treatment often necessary nutritional support
Offloading	Type and site of wound biomechanical evaluation	Protectic/therapeutic footwear
	Mobility/walking capacity	Insoles/ortosis
		Total contact cast/walkers Crutches wheelchair bed rest
Wound bed preparation	Type, site, condition of the ulcer necrosis/debris exudation peri-wound maceration signs of inflammation granulation	Topical treatment/dressings debridement removal of debris
		Control of exudation, moist wound healing, control of infection NWPT therapy tissue engineering/growth factors, matrix modulation
Removal of dead tissue	Extent of tissue destruction	Incision/drainage/amputation
	Infection ischaemia	
Correction of foot deformities	Evaluation of foot deformities	Corrective foot surgery,skin transplant/pinch graft amputation
Improve general condition	Dehydration/malnutrition	Fluid and nutrition replacement therapy
	Intercurrent disease	Aggressive treatment of intercurrent disease antiplatelet drugs, antihypertensive agents, lipid decreasing agents Cessation of smoking physiotherapy
	Congestive heart failure, nephropathy	
	Metabolic syndrome	
	Smoking habits	
	History of abuse	

ESR erythrocyte sedimentation rate, *CRP* C-reactive protein, *CT* computed tomography, *GCSF* granulocyte-colony stimulating factor, *MRT* magnetic resonance imaging, *NWPT* negative wound pressure therapy

Vascular clinical examination

Pulse palpation is the cornerstone of vascular examination and gives information about the circulatory status above the palpation level but not distally. The absence of pedal pulses have been shown to indicate the presence of peripheral vascular disease and poor primary healing of the ulcers at least in half of the patients [48–53]. Yet, pulse palpation is not necessarily a method of good reproducibility [48–53].

Non-invasive vascular studies: special considerations related to diabetic foot

There is a number of methods used to assess macrocirculation in order to identify legs that are not viable or lesions

that do not heal [31, 49, 54–70]. Indications for vascular consultation include ankle/brachial index (ABI) <0.7 and toe blood pressure <40 mmHg according to Clinical Practice Guidelines for Diabetic Foot Disorders of American College of Foot and Ankle Surgeons [71]. ABI <0.4–0.45, absolute systolic ankle pressure <55 mmHg and toe pressure <30 mmHg have been most frequently used to indicate need for revascularisation [67, 71]. However, the ABI might underestimate PAD prevalence in diabetic patients because of the calcifications of the arteries ankle pressures may be spurious in up to 40% of all diabetic subjects due to arterial calcification and non-compressibility [59, 72]. A non-measurable ankle pressure due to non-compressible arteries has also been related to poor outcome (amputation, death).

The systolic toe pressure may give more reliable information of the level of distal flow capacity [59]. A systolic toe pressure level of <30–50 mmgHg is related to a high probability of amputation and presence or development of gangrene. The systolic toe pressure have been related to increased probability of healing in cohort studies of individuals with diabetes and neuropathic and neuroischemic ulcers [16, 31, 56, 57, 71, 72]. However, toe pressure measurements usually assess only the great toe and cases have described patients with a non-measurable toe blood pressure due to incompressible arteries [31, 56].

A transcutaneous oxygen pressure (tcpO2) below 30 mmHg or at least below 20 mmHg has been considered to predict that the infection will not resolve and the ulcer not heal [58, 59, 69], but more frequently used as a surrogate marker for amputation level selection [59, 61, 62]. In a recent systematic review, a peri-wound PtcO2 level below a cutoff of 20 or 30 mmHg was an independent predictor of chronic wound healing complications. However, no further conclusions could not be made due to the limited number of studies, as well as possible reporting bias, and heterogeneity [71].

The accuracy of these measurements in patients with critical leg ischaemia has been questioned, especially in the presence of tissue oedema [60].

Low levels of ABI, ankle pressure, toe pressure and tcPO2 suggest that diabetic ulcer may not heal, but always in the consideration of limitations of each technique [31, 72].

Vascular imaging

When non-invasive diagnostics so indicate, imaging of the arterial tree, especially crural and pedal arteries, should be performed. This may be done by Duplex ultrasound, magnetic resonance angiography (MRA), computed tomography angiography (CTA) or digital subtraction angiography (DSA) [73–78]. Imaging is of key importance in the decision how to treat the arterial lesions [73]. In diabetics, aortoiliac arteries and common femoral artery are often and even superficial femoral artery may be unaffected and occlusive lesions are concentrated to distal parts of lower limb arterial tree [70, 79]. Extensive calcification of infrapopliteal arterial tree may prevent proper Duplex diagnostics and CTA although the use of multisliced devices decreases interpretation difficulties caused by arterial wall calcifications [67, 78].

In diabetics with foot ulcer chronic renal failure is increasingly common [80]. Metformin should be stopped before angiography as it may cause lactic acidosis [81]. Renal insufficiency influences the choice of imaging method, because contrast media are nephrotoxic agents [82–84]. In the case of mild chronic renal failure, regular DSA and CTA can be done, but intravenous hydration of the patient is recommended before and after the examination [73, 79]. Detailed visualisation of infrapopliteal arteries, including the arteries of the foot, is necessary for complete evaluation of diabetic patients [49, 72, 73].

Revascularisation

There is a general agreement that surgical treatment is indicated to relive symptoms of limb-threatening ischaemia including ischemic pain, ischemic ulcers and gangrene [3, 40, 42, 47]. These patients constitutes a severe challenges due to the presence of co-existent and co-morbidity (cardiocerebrovascular disease, nephropathy) and the possibility for intervention is strongly related to the presence/extent of co-morbidity more than availability for intervention according to angiography [2, 85–88].

Endovascular therapy for infrapopliteal arterial disease is gaining acceptance as a first line revascularisation method to improve ulcer healing and limb salvage [89–96]. The angioplasty of isolated crural arterial lesions in diabetic patients with unhealed ulcer is also considered as an effective and safe therapeutic modality to avoid limb loss [90]. An important task of any revascularisation is to achieve at least one open infrapopliteal artery down to the foot, preferably the artery that supplies the anatomical region of the ulcer [89, 97–100]. The revascularisation of plantar arch and branches of peroneal artery has been suggested recently [97–100]. There are few studies evaluating wound healing and amputation rate after revascularisation in diabetic patients with neuroischemic or ischemic ulcers [2, 85, 88].

Bypass surgery and/or subintimal recanalisation should be attempted in patients if PTA is not possible or not successful [101–103]. There is not a single randomized controlled trial available comparing endovascular and surgical revascularisation in the treatment of impaired

perfusion or critical ischaemia in diabetics [88]. A systematic review revealed seven case series on revascularisations exclusively for diabetic foot provided that all were diabetics, all had ulcer and all were treated with an infrainguinal revascularisation [88]. Bypass surgery and endovascular interventions are therefore complementary techniques for revascularizarion in diabetic patients with non-healing ulcer [72].

Pharmacological intervention to improve perfusion

The benefits of pharmacological treatment to improve perfusion remain controversial [2, 4]. Treatment to remove peripheral oedema focused on causative factor (congestive heart failure, nephropathy, infection or hydrostatic/neuropathic oedema) is mandatory. A number of pharmacological substances have been studied as to ulcer healing [104–106]. The use of heparin subcutaneously has shown promising results in small RCTs of neuroischemic foot ulcers in patients with diabetes not available for revascularisation [104]. However, all these studies are too limited to allow any recommendations. Gene therapy and the use of oxygenic growth factors to stimulate development of collaterals is under development but still unproven in the clinical setting [107, 108].

Diabetic foot infection

Infection is seldom the direct cause of ulcer but strongly related to probability for amputation especially in combination with PAD [2, 3, 14, 16, 109]. Often there is a combination of ischaemia and infection among events leading to amputation in the diabetic foot [14, 16, 110]. In the EURODIALE study, 25–75% of patients at various centres were considered to have a wound infection at the time of admission [14]. An infection in the diabetic foot is a limb-threatening condition and was the immediate cause for amputation in 25–50% of diabetic patients [10, 109, 111].

In several studies, the outcome of deep foot infection has been related to the extent of tissue involved, co-morbidity and co-existing peripheral arterial disease [14, 16, 109].

Once an ulcer is complicated by an infection, the risk for subsequent amputation is greatly increased. In a study by Lavery et al. [112] factors related to the development of a wound infection were duration of ulcer >30 days, recurrent ulcer, trauma, probing to bone and co-existent PAD. Deep infections are manifested either as osteomyelitis or a soft tissue infection spreading along the tendons in the compromised foot [109–111].

Foot infection: diagnosis and evaluation of extent of tissue involvement

Wound infections are diagnosed clinically and mostly on the basis of local signs and symptoms of inflammation. Clinical signs of the infection can be reduced due to diminished leucocyte function, peripheral arterial disease, poor metabolic control and neuropathy [109, 111, 113]. In almost 50% of patients with diabetes and deep foot infections signs such as increased white blood cell count, erythrocyte sedimentation rate (ESR), C-reactive protein concentration (CRP) and body temperature were absent resulting in delay in diagnosis and optimal treatment [109, 111, 113, 114]. The most common sign of foot infection in individuals with diabetes and an ulcer was increased exudation rate [109]. Some patients with diabetic foot infection also have a worsening of their glycaemic control but other blood tests are not exclusive. A swollen foot with long-term ulceration or a red swollen digit should always arouse suspicion of infection with extension to deep tissue with or without osteomyelitis. Indeed, the severity of infection should be assessed after debridement of callus and necrotic tissue, based on its extent and depth as well as the presence of any systemic findings [111, 113, 114].

Continuous extension of soft tissue infection to underlying bone poses both diagnostic and therapeutic challenges [111, 114–116]. Imaging studies may help diagnose or better define deep, soft tissue purulent collections and are usually needed to detect pathological findings in bone [114–116]. Plain radiographs of the foot may be of value to reveal the presence of a foreign body, gas, osteolysis or joint effusion. Radiological diagnosis is often difficult because changes suggesting osteomyelitis usually takes several weeks to become visible on X-ray. The difficulty in distinguishing osteomyelitis from osteoarthropathy or fracture is well recognized. To evaluate the presence of and extent of a deep foot infection bone scan, MRI or CT can be of value [114–116]. Blood tests are of limited use but fever with an increased ESR, white cell count and CRP are usually helpful in recognising soft tissue infections or abscess [110, 114, 115]. Conclusive diagnosis of osteomyelitis can be obtained by bone biopsy [114–117].

Antimicrobial treatment

Antibiotic therapy is considered necessary for virtually all infected wounds, but it is not beneficial for non-infected ulcers. Antibiotic therapy is often insufficient without appropriate wound care [2].

When infection is suspected a microbiological diagnosis will usually assist subsequent management. In an acute superficial infection, Gram-positive cocci are the most common pathogen [109–116]. Several studies have confirmed that

in 'chronic lesions', ulcers with a deep infection and in wounds with necrotic tissue a polymicrobial flora is most common, with a combination of Gram negative, anaerobic and Gram-positive organisms especially in patients who have received prior antibiotic treatment [109–116].

Among studies comparing different antibiotic regimens in the management of skin and soft tissue infection or, infection that involved both soft tissue and bone, one reported a better clinical outcome with use of cefoxitin rather than ampicillin/sulbactam, but the others reported no differences between treatment strategies [118–137]. Substantial limitations in most studies [2, 114, 116, 138] evaluating the efficacy of antimicrobial agents with a high risk of bias [2]. As a consequence, the initial antimicrobial treatment as well as duration of treatment is empiric.

An empirical antibiotic regimen for diabetic foot infection should be based on an understanding of anti-infective principles, the most important of which is the extent and severity of infection [2, 114, 116, 138]. This also dictates the mode of antibiotic administration. Therapy aimed solely at aerobic Gram-positive cocci may be sufficient for acute mild-to-moderate infections in patients who have not recently received antibiotic therapy [2, 114, 116]. In long standing ulcers or ulcer with delayed healing with ischaemia or necrotic tissue frequently a polymicrobial flora is present in which the causative agent is unknown. Broad spectrum empirical therapy is not routinely required but is indicated for moderate to severe infections [111, 113, 114]. Definitive therapy should be based on both the culture results and susceptibility data and clinical response to the empirical regimen. Antibiotic therapy is continued until there is evidence that the infection has resolved but not necessarily until a wound has healed [2, 58, 111, 113, 114, 116]. If the wound infection is suspected appropriately obtained specimens should be collected after wound debridement for culture prior to starting empirical antibiotic therapy in all cases of infection. Tissue specimens can be obtained by biopsy, ulcer curettage, or aspiration and are preferable to wound swab specimens [2, 111, 113, 114, 116].

A meta-analysis of the adjunctive use of granulocyte-colony stimulating factor (G-CSF) in diabetic foot infections concluded that adding G-CSF did not significantly affect the likelihood of resolution of infection or wound healing, although it was associated with a reduced likelihood of lower extremity surgical interventions, including amputation [139–143].

Medical or surgical intervention in diabetic foot infections

Infections accompanied by a deep abscess, extensive bone or joint involvement, crepitus, substantial necrosis or gangrene, or necrotizing fascitis need prompt surgical consultation. Spreading of infection in diabetic foot can be extremely rapid and it may lead to life threatening general septic infection if treatment is delayed. Urgent evaluation of lower limb circulation, treatment of infections and surgical procedures, including debridements and revascularisations, are often needed as first line leg salvage procedures [144].

Choosing between medical and surgical therapy in osteomyelitis is difficult and unclear. Traditionally, it has been thought that the essential cure is resecting a bone with chronic osteomyelitis. Yet, such surgical solutions as ray and metatarsal amputations alter the structure and biomechanics of the foot creating new problems. Available evidence suggests that if those who need urgent surgery for life-or limb-threatening infection are excluded, surgical debridement of infected bone may not be routinely necessary and arrest of infection may be achieved with antibiotics alone [145]. There is accumulating evidence that surgical debridement of infected bone is not routinely necessary [29, 57]. However, in a review of antimicrobial treatment the combined observed treatment failure was 22.7% in 18 RCTs comparing various antibiotics in diabetic foot infections and treatment failure was similar in patients with and without osteomyelitis 26.5% 44/169 vs 23.2% 330/1,424 [146].

The most important step in the control of deep infection is urgent incision and drainage of an abscess and radical debridement of all infected, non-viable necrotic tissue. The debridement should be done first and in the case of ischaemia, revascularisation thereafter. Distal bypass, when needed, is usually delayed 2–5 days to control the infection [113, 129, 130, 147].

In situations without a limb-threatening infection, the blood supply to the wound/extremity should be optimised before surgical debridement to ensure that potentially viable tissue is not unnecessarily removed [147, 148].

Diabetic foot ulcers and co-morbidity

Large cohort studies have given us a deeper understanding regarding factors related to outcome in case of a diabetic foot ulcer. Co-morbidity increases significantly with the severity of foot disease and is strongly related to the outcome [13, 16, 31, 32, 149]. It is important to differentiate between neuropathic and neuroischemic ulcers with regard to factors related to outcome and extent of co-morbidity [13, 16, 56].

These studies show the importance of co-morbidities like cardiovascular disease, end stage renal disease, severity of PAD, extent of tissue involvement and lower leg oedema for the outcome (primary healing and healing

with or without minor amputation, respectively) [13, 16, 56, 80, 149]. It is of utmost importance to recognize that the diabetic foot ulcer is a sign of multiorgan disease.

Aggressive medical treatment with regard to co-morbidity including measures to improve the metabolic control, nutrition, aid cessation of smoking, treatment of hypertension and dyslipidemia and adjuvant treatment with anti-platelet drugs is mandatory in the management of the metabolic syndrome and intercurrent disease [150].

Diabetic foot ulcer and wound healing/treatment

Debridement

The choice and timing of debridement techniques in the diabetic foot can be described in terms of initial damage control to save the leg and the life of the patient, secondary eradication of devitalised tissue to improve or facilitate wound healing [2, 151, 152]. The need for and choice of technique of debridement is dependent on the level of decreased perfusion to the foot and the extent of tissue loss, not only to achieve healing of an ulcer, but also to maintain ambulation. The method of debridement including surgical, enzymatic, biological or autolytic is choosable and more than one debridement method may be appropriate [151, 152]. Several non-surgical debridement techniques have been suggested, not only to remove dead tissue when surgery is not favourable/advisable, or to change/improve the condition of the wound to increase the probability of healing and shorten wound healing time [151, 152]. There are no convincing data to prove if any of the methods available is better than others with regard to probability of healing according to Cochrane Database [151, 152].

From pragmatic point of view, the message is in case infection always surgical debridement preferable, in case of ischaemia revascularisation first debridement later in ulcers with limited amount of available soft tissue non-surgical techniques might be preferable with regard to extent of tissue loss to achieve healing and maintain a foot that is ambulative following healing. Surgery is always the quickest way of debridement but related to the most extensive tissue loss. Heel ulcers are especially vulnerable as poor perfusion in the heel fat pad and danger of debriding into calcaneus may expose the area for deep infection.

Choice of dressings or topical treatment to improve the condition of the wound

In patients with diabetes mellitus, there is a substantial delay in wound healing which has been considered to be related to several abnormalities such as decreased concentrations of growth factors, increased protease activity, abnormalities of the extracellular matrix-reduced fibroblast function and impaired nutritive function [21, 22, 153]. Most of these factors have been related to hyperglycaemia, several new treatments related to these abnormalities have been explored in wound healing such as various growth factor products, hyaluronic acid, matrix modulators, skin tissue engineering products artificial skin. Encouring results have been presented but at the moment there is no consensus regarding indications for and value of these treatments [107, 108, 154]. The basic principles for choice of topical treatment in diabetic foot ulcers are comparable to other kind of wounds with exceptions that the lesions are frequently located on weight bearing areas, frequently lack of skin sensation, increased risk of infection and ischaemia.

Negative pressure wound therapy

Negative pressure wound therapy (NPWT) has shown promising results in improving wound condition in diabetes subjects with cavity ulcers and ulcers after a for foot amputation [155–160]. Two randomised controlled studies have shown reduced wound area, improved wound healing rate in patients with foot ulcer and adequate circulation compared to controls in 16 week trials [155, 159]. The application of vacuum-assisted negative pressure across the wound surface leads to a number physiological and biochemical changes. It has been suggested that the application of NPWT can support wound healing by removing excess exudates levels, promote granulation tissue, provide a closed environment, stimulate granulation tissue, reduce oedema and increase local blood flow [160].

The prerequisite for optimal effect is that there is sufficient blood supply for ulcer healing. NPWT does neither replace surgical wound debridement, measures to improve blood circulation nor relevant treatment of infection [160]. However, NPWT therapy has to be performed by health care staff with adequate skill since the technique is not without adverse reactions and its essential to chose the right ulcer with adequate perfusion and control of infection.

Hyperbaric oxygen therapy

Hyperbaric oxygen therapy given as adjunct to other therapy may reduce the risk of major amputation related to diabetic foot ulcer [161–168]. In previous RCT's, the healing of ulcers and prevention of amputations seemed to be connected to lesions with ischaemia and/or infection [85, 137, 139–143]. Yet, conclusions were uncertain as the series were small and methodologically deficient [161–166]. Recently, a double-blind RCT demonstrated significantly improved outcome in the intervention group as treated patients were more likely to heal within 12 months: 25/48 (52%) vs 12/42 (27%); $p = 0.03$ [167]. Although

this study had limitations including patient population, some with adequate perfusion and others with unreconstructable ischaemia, its potential implications are far-reaching and the study needs to be repeated with full health economic analysis, and with an attempt being made to define the population most likely to benefit [168].

Off loading—non weight-bearing

Whatever the primary cause, continuous walking on insensitive foot impairs subsequent healing and inadequate tissue perfusion impairs tissue viability and prevents ulcer healing. The most important feature of the treatment of any ulcer with neuropathy is to restrict weight bearing, irrespective of the presence of ischaemia.

Many interventions with advanced wound management have failed due to failing recognition of the need for effective offloading [169, 170]. The aim of offloading and protection is to maintain ambulation and treat the foot ulcer. In the acute situation crutches, wheelchair or bed rest might be necessary.

In most situations an adequately fitting shoe, orthosis or insoles will be sufficient. However, in cases with plantar ulceration, in which disturbed biomechanic pressures cause deteriorated circulation, techniques to decrease plantar peak pressure is necessary including total contact cast (TCC), walkers, removable or non-removable, or other devices [171].

Studies indicate that the offloading system has to achieve a threshold of a peak pressure <200 KPa to maintain healing [172]. This requires shoes provided by orthopaedic specialist clinic and the patient requires shoes for both indoor and outdoor use [169–171]. Acceptable techniques used in offloading include soft and shock-absorbing materials, custom moulding, forefoot or heel offloading shoes, rocker-bottom shoes, casts, walkers, crutches, wheelchair and surgery [169–171].

Randomised controlled trials have shown that the TCC is more effective than removable devices both with regard to plantar foot ulcer healing and time to heal [173, 174]. Removable walkers that have been made non-removable may be as effective as TCC and more effective than standard removable walkers in healing plantar ulcers [171, 173, 174]. Conventional standard therapeutic footwear is not effective in ulcer healing [171]. The role of custom footwear in this context is not yet clear. If foot wear cannot heal or prevent recurrent ulceration, then the patients' activity level must be drastically modified [169–171].

Foot surgery, correction of deformities and amputation

Some data exist to support the use of surgical techniques to offload a non-infected neuropathic ulcer, including surgical excision of ulcers, arthroplasties, metatarsal head resections and Achilles tendon lengthening. Combined with local skin flap, when needed, these procedures seem to give good results, if tissue perfusion is adequate [175–181]. These techniques seem to contribute to improve the time to healing rather than the eventual rate of healing as well as to reduce the risk of ulcer recurrence. Elective surgery should be considered to correct structural deformities that cannot be accommodated by therapeutic footwear. Common procedures include hammertoe repair, metatarsal osteotomies, plantar exostectomies and Achilles tendon lengthening [175, 177, 181]. Complicated Charcot surgery is also a part of offloading indicated for chronic recurrent ulcerations and joint instability when patients present with unstable or displaced fracture dislocations [182].

Patients with restricted gangrene or dry necrotic lesions usually benefit from revascularisation first. Often patients need several debridements and long care of several months before ulcers have healed even after successful revascularisation [144, 147].

The major adverse outcome for diabetic foot problems is a lower leg amputation. The indications for amputation in patients with diabetes are often multiple [2], the indications most commonly cited are gangrene and infection frequently occurring simultaneously. In some studies, a non-healing ulcer has also been claimed as an indication [2]. It has to be emphasised that a non-healing ulcer in itself should not be considered an indication for amputation since long duration is not an unfavourable factor with regard amputation as long as duration of ulcer in itself is not considered an indication [2, 3]. However, there is established a correlation between duration of ulcer and probability for healing within 12 weeks in trials of neuropathic foot ulcer [71].

There is still some controversy concerning the benefit of a primary minor amputation vs primary major amputation (below knee) [147, 183]. The advantage of primary major amputation is a lower reamputation rate and shorter healing time [183]. Minor amputations are associated with higher reamputation rate and as a consequence longer wound healing time. However, in a prospective study, the long-term outcome after a healed index amputation in patients with diabetes and foot ulcer was evaluated and it was concluded that those subjects with an index major amputation had a higher mortality rate, an equal rate of new amputations irrespective of level, an increased rate of new contralateral amputations and a lower potential for rehabilitation than patients with an index minor amputation [186].

Conclusions

It should be recognized that the diabetic foot ulcer is a sign of an underlying multiorgan disease.

Treatment of the diabetes foot ulcer requires a multidisciplinary approach due to the complexity of factors related to outcome.

There is a need to introduce and recognize decreased perfusion or impaired circulation as indicator for the need of revascularisation in the diabetic foot to achieve healing.

Bypass surgery and endovascular interventions are complementary techniques for revascularisation in diabetic patients with non-healing ulcer.

Clinical signs of the infection can be reduced. Imaging studies may help to define deep, soft tissue infection and are frequently needed to detect pathological findings in bone.

An empirical antibiotic regimen for diabetic foot infection should be based on an understanding of anti-infective principles, the most important of which is the extent and severity of infection.

The need for and choice of technique of debridement is dependent on the level of decreased perfusion to the foot and the extent of tissue loss, not only to achieve healing of an ulcer, but also to maintain ambulation.

In patients with diabetes mellitus, there is a substantial delay in wound healing. Several new treatments related to these abnormalities have been explored in wound healing.

NPWT has shown promising results in improving wound condition in diabetes subjects with cavity ulcers and ulcers after a for foot amputation.

Randomised controlled trials have shown that the TCC is more effective than removable devices both with regard to plantar foot ulcer healing and time to heal.

References

1. A.J. Boulton, L. Vileikyte, G. Ragnarson-Tennvall, J. Apelqvist, The global burden of diabetic foot disease. Lancet **366**(9498), 1719–1724 (2005)
2. International Working Group on the Diabetic Foot, International consensus on the diabetic foot and practical guidelines on the management and the prevention of the diabetic foot. Amsterdam, the Netherlands (2011). Available on CD-ROM at www.idf.org/bookshop or (www.diabeticfoot.nl)
3. J. Apelqvist, K. Bakker, W.H. van Houtum, International Working Group on the Diabetic Foot (IWGDF) Editorial Board, Practical guidelines on the management and prevention of the diabetic foot: based upon the International Consensus on the Diabetic Foot (2007) prepared by the International Working Group on the Diabetic Foot. Diabetes Metab. Res. Rev. **24**(Suppl 1), S181–S187 (2008)
4. S. Tesfaye, A.J.M. Boulton, P.J. Dyck, R. Freeman, M. Horowitz, P. Kempler et al., Diabetic neuropathies: update on definitions, diagnostic criteria, estimation of severity, and treatments. Diabetes Care **33**(10), 2285–2293 (2010)
5. E.J. Boyko, J.H. Ahtoni, V. Stensel, R.C. Forsberg, D.R. Davignon, D.G. Smith, A prospecticve study for risk factors for diabetic ulcer. The Seattle Diabetic Foot Study. Diabetes Care **22**, 1036–1042 (1999)
6. C.A. Abbott, A.L. Carrington, H. Ashe, S. Bath, L.C. Every, J. Griffiths et al., The North-West Diabetes Foot Care Study: incidence of, and risk factors for, new diabetic foot ulceration in a community-based patient cohort. Diabet. Med. **19**, 377–384 (2002)
7. N. Singh, D.G. Amstrong, B.A. Lipsky, Preventing foot ulcers in patients with diabetes. JAMA **293**, 217–228 (2005)
8. E.J. Boyko, J.H. Ahroni, V. Cohen, K.M. Nelson, P.J. Heagerty, Prediction of diabetic ulcer occurrence using commonly available clinical information. The Seattle Diabetic Foot Study. Diabetes Care **29**, 1202–1207 (2006)
9. A.J. Boulton, The diabetic foot: grand overview, epidemiology and pathogenesis. Diabetes Metab. Res. Rev. **24**(Suppl 1), S3–S6 (2008)
10. J. Apelqvist, J. Larsson, What is the most effective way to reduce incidence of amputation in the diabetic foot? Diabetes Metab. Res. Rev. **16**(Suppl 1), S75–S83 (2000)
11. W. Jeffcoate, F. Game, P. Cavanagh, The role of proinflammatory cytokines in the cause of neuropathic osteoartropathy (acute Charcot foot) in diabetes. Lancet **366**, 2058–2061 (2005)
12. E. Trepman, A. Nihal, M. Pinzur, Charcot neuroarthropathy of the foot and ankle. Foot Ankle Int. **26**, 46–63 (2005)
13. L. Prompers, N. Schaper, J. Apelqvist, M. Edmonds, E. Jude, D. Mauricio et al., Prediction of outcome in individuals with diabetic foot ulcers: focus on the differences between individuals with and without peripheral arterial disease. The EURODIALE study. Diabetologia **51**(5), 747–755 (2008)
14. L. Prompers, M. Huijberts, J. Apelqvist, E. Jude, A. Piaggesi, K. Bakker, M. Edmonds, P. Holstein, A. Jirkovska, D. Mauricio, G. Ragnarson Tennvall, H. Reike, M. Spraul, L. Uccioli, V. Urbancic, K. Van Acker, J. van Baal, F. van Merode, High prevalence of ischaemia, infection and serious comorbidity in patients with diabetic foot disease in Europe. Baseline results from the Eurodiale study. Diabetologia **50**, 18–25 (2007)
15. L. Prompers, M. Huijberts, J. Apelqvist, E. Jude, A. Piaggesi, K. Bakker, M. Edmonds, P. Holstein, A. Jirkovska, D. Mauricio, G.R. Tennvall, H. Reike, M. Spraul, L. Uccioli, V. Urbancic, K. Van Acker, J. Van Baal, F. Van Merode, N. Schaper, Delivery of care to diabetic patients with foot ulcers in daily practice: results of the Eurodiale study, a prospective cohort study. Diabet. Med. **25**, 700–707 (2008)
16. M.A. Gershater, M. Löndahl, P. Nyberg, J. Larsson, J. Thörne, M. Eneroth, J. Apelqvist, Complexity of factors related to outcome of neuropathic and neuroischaemic/ischaemic diabetic foot ulcers: a cohort study. Diabetologia **52**(3), 398–407 (2009)
17. N.C. Schaper, M.H. Nabuurs-Franssen, S.P. Huijberts, Peripheral vascular disease and type 2 diabetes mellitus. Diabetes Metab. Res. Rev. **16**(Suppl 1), S11–S15 (2000)
18. F.W. LoGerfo, J.D. Coffman, Current concepts. Vascular and microvascular disease of the foot in diabetes. Implications for foot care. N. Engl. J. Med. **311**, 1615–1619 (1984)
19. G. Jörneskog, K. Brismar, B. Fagrell, Pronounced skin capillary ischemia in the feet of diabetic patients with bad metabolic control. Diabetologia **41**(4), 410–415 (1998)
20. N.C. Schaper, M. Huijberts, K. Pickwell, Neurovascular control and neurogenic inflammation in diabetes. Diabetes Metab. Res. Rev. **24**(suppl 1), S40–S44 (2008)
21. M.S. Ruiter, J.M. van Golde, N.C. Schaper, C.D. Stehouwer, M.S. Huijberts, Diabetes impairs arteriogenesis in the peripheral circulation: review of molecular mechanisms. Clin. Sci. (Lond.) **119**(6), 225–238 (2010)
22. C. Gazzaruso, A. Coppola, M. Montalcini, E. Baffero, A. Garzaniti, G.G. Pelissero, S. Collaviti, A. Grugnetti, P. Gallotti, A. Pujia, S.B. Solerte, A. Giustina, Lipoprotein(a) and homocysteine as genetic risk factors for vascular and neuropathic diabetic foot in type 2 diabetes mellitus. Endocrine **41**, 89–95 (2012)

23. L. Prompers, M. Huijberts, J. Apelqvist, E. Jude, A. Piaggesi, K. Bakker et al., Optimal organization of health care in diabetic foot disease: introduction to the Eurodiale study. Int. J. Low Extrem. Wounds **6**(1), 11–17 (2007)
24. S. Krishnan, F. Nash, N. Baker, D. Fowler, G. Rayman, Reduction in diabetic amputations over 11 years in a defined U.K. population: benefits of multidisciplinary team work and continuous prospective audit. Diabetes Care **31**, 99–101 (2008)
25. W.H. van Houtum, J.A. Rauwerda, D. Ruwaard, N.C. Schaper, K. Bakker, Reduction in diabetes-related lower-extremity amputations in the Netherlands: 1991–2000. Diabetes Care **27**, 1042–1046 (2004)
26. J. Larsson, J. Apelqvist, C.D. Agardh, A. Stenström, Decreasing incidence of major amputation in diabetic patients: a consequence of a multidisciplinary foot care team approach? Diabet. Med. **12**, 770–776 (1995)
27. K. Aydin, M. Isildak, J. Karakaya, A. Gurlek, Change in amputation predictors in diabetic foot disease: effect of multidisciplinary approach. Endocrine **38**, 87–92 (2010)
28. M. Luther, I. Kantonen, M. Lepantalo, FINNVASC Study Group, Arterial intervention and reduction in amputation for chronic critical leg ischaemia. Br. J. Surg. **87**, 454–458 (2000)
29. H. Zayed, M. Halawa, L. Maillardet, P.S. Sidhu, M. Edmonds, H. Rashid, Improving limb salvage rate in diabetic patients with critical leg ischaemia using a multidisciplinary approach. Int. J. Clin. Pract. **63**(6), 855 (2009)
30. A.J.M. Boulton, The diabetic foot: from art to science. Diabetologia **47**(8), 1343–1353 (2004)
31. International Working Group on the Diabetic Foot (IWGDF) Editorial Board, The diabetic foot. Diabetes Metab. Res. Rev. **24**(Suppl 1), S1–S193 (2008)
32. P.R. Cavanagh, B.A. Lipsky, A.W. Bradbury, G. Botek, Treatment for diabetic foot ulcers. Lancet **366**(9498), 1725–1735 (2005)
33. J. Kalish, A. Hamdan, Management of diabetic foot problems. J. Vasc. Surg. **51**(2), 476–486 (2010)
34. J. Apelqvist, The foot in perspective. Diabetes Metab. Res. Rev. **24**(Suppl 1), S110–S115 (2008)
35. D. Steed, C. Attinger, T. Colaizzi, M. Crossland, M. Franz, L. Harkless et al., Guidelines for the treatment of diabetic ulcers. Wound Repair Regen. **14**, 680–692 (2006)
36. S. Vuorisalo, M. Venermo, M. Lepäntalo, Treatment of diabetic foot ulcers. J. Cardiovasc. Surg. **50**(3), 275–291 (2009)
37. R. Fontaine, M. Kim, R. Kieny, Surgical treatment of peripheral circulation disorders. Helv. Chir. Acta **21**, 499–533 (1954)
38. P.R.F. Bell, D. Charlesworth, R.G. DePalma, H.H.G. Eastcott, B. Eklöf, J.D. Gruss, C.W. Jamieson, P.J. Morris, A.N. Nicolaides, R.B. Rutherford, The definition of critical iscaemia of a limb. Br. J. Surg. **69**, 22 (1982)
39. Suggested standards for reports dealing with lower extremity ischemia, Prepared by the Ad Hoc Committee on Reporting Standards, Society for Vascular Surgery/North American Chapter, International Society for Cardiovascular Surgery. J. Vasc. Surg. **4**(1), 80–94 (1986)
40. Second European consensus document on chronic critical leg ischaemia. Eur. J. Vasc. Surg. **6**(suppl A), 1–32 (1992)
41. R.B. Rutherford, J.D. Baker, C. Ernst, K.W. Johnston, J.M. Porter, S. Ahn, D.N. Jones, Recommended standards for reports dealing with lower extremity ischemia: revised version. J. Vasc. Surg. **26**(3), 517–538 (1997)
42. L. Norgren, W.R. Hiatt, J.A. Dormandy, on behalf of the TASC II Working Group, Inter-society consensus for the management of peripheral arterial disease (TASC II). J. Vasc. Surg. **45**(Suppl), S5–S67 (2007)
43. Management of peripheral arterial disease (PAD), Transatlantic inter-society consensus (TASC). Eur. J. Vasc. Endovasc. Surg. **19**(Suppl A), S1–S250 (2000)
44. N.C. Schaper, Diabetic foot ulcer classification system for research purposes: a progress report on criteria for including patients in research studies. Diabetes Metab. Res. Rev. **20**(Suppl 1), 90–95 (2004)
45. D.G. Armstrong, L.A. Lavery, L.B. Harkless, Validation of a diabetic wound classification system. The contribution of depth, infection, and ischemia to risk of amputation. Diabetes Care **21**(5), 855–859 (1998)
46. S. Beckert, M. Witte, C. Wicke et al., A new wound-based severity score for diabetic foot ulcers. Diabetes Care **29**(5), 988–992 (2006)
47. N.C. Schaper, G. Andros, J. Apelqvist, K. Bakker, J. Lammer, M. Lepantalo, J.L. Mills, J. Reekers, C.P. Shearman, R.E. Zierler, R.J. Hinchliffe, Diagnosis and treatment of peripheral arterial disease in diabetic patients with a foot ulcer. A progress report of the International Working Group on the Diabetic Foot. Diabetes Metab. Res. Rev. **28**(Suppl 1), 218–224 (2012)
48. S.R. McGee, E.J. Boyko, Physical examination and chronic lower-extremity ischemia: a critical review. Arch. Intern. Med. **158**(12), 1357 (1998)
49. N.C. Schaper, G. Andros, J. Apelqvist, K. Bakker, J. Lammer, M. Lepantalo, J.L. Mills, J. Reekers, C.P. Shearman, R.E. Zierler, R.J. Hinchliffe, Specific guidelines for the diagnosis and treatment of peripheral arterial disease in a patient with diabetes and ulceration of the foot. Diabetes Metab. Res. Rev. **28**(Suppl 1), 236–237 (2012)
50. M. Lundin, J.P. Wiksten, T. Peräkylä, O. Lindfors, H. Savolainen, J. Skyttä et al., Distal pulse palpation: is it reliable? World J. Surg. **23**, 252–255 (1999)
51. J. Apelqvist, J. Larsson, C.-D. Agardh, The importance of peripheral pulses, peripheral oedema and local pain for the outcome of diabetic foot ulcers. Diabet. Med. **7**, 590–594 (1990)
52. G. Andros, R.W. Harris, L.B. Dulawa, R.W. Oblath, S.X. Salles-Cunha, The need for arteriography in diabetic patients with gangrene and palpable foot pulses. Arch. Surg. **119**(11), 1260–1263 (1984)
53. E.J. Boyko, J.H. Ahroni, D. Davignon, V. Stensel, R.L. Prigeon, D.G. Smith, Diagnostic utility of the history and physical examination for peripheral vascular disease among patients with diabetes mellitus. J. Clin. Epidemiol. **50**(6), 659–668 (1997)
54. A.M. O'Hare, R. Katz, M.G. Shilipak, M. Cushman, A.B. Newman, Mortality and cardiovascular risk across ankle-arm index spectrum: results from the Cardiovascular Health Study. Circulation **113**, 388–393 (2006)
55. V. Aboyans, E. Ho, J.O. Denenberg, L.A. Ho, L. Natarajan, M.H. Criqui, The association between elevated ankle systolic pressures and peripheral occlusive arterial disease in diabetic and nondiabetic subjects. J. Vasc. Surg. **48**, 1197–1203 (2008)
56. J. Apelqvist, J. Castenfors, J. Larsson, A. Stenstrom, C.D. Agardh, Prognostic value of systolic ankle and toe blood pressure levels in outcome of diabetic foot ulcer. Diabetes Care **12**, 373–378 (1989)
57. P. Holstein, The distal blood pressure predicts healing of amputations on the feet. Acta Orthop. Scand. **55**, 227–233 (1984)
58. J.L. Ballard, C.C. Eke, T.J. Bunt, J.D. Killeen, A prospective evaluation of transcutaneous oxygen measurements in the management of diabetic foot problems. J. Vasc. Surg. **22**, 485–490 (1995)
59. E. Faglia, G. Clerici, M. Caminiti, A. Quarantiello, V. Curci, A. Morabito, Predictive values of transcutaneous oxygen tension for above-the-ankle amputation in diabetic patients with critical limb ischemia. Eur. J. Vasc. Endovasc. Surg. **33**, 731–736 (2007)
60. E. Lukkari-Rautiarinen, M. Lepäntalo, J. Pietilä, Reproducibility of skin blood flow, perfusion pressure and oxygen tension

measurements in advanced lower limb ischaemia. Eur. J. Vasc. Surg. **3**, 345–350 (1989)
61. M.S. Pinzur, R. Stuck, R. Sage, H. Osterman, Transcutaneous oxygen tension in the dysvascular foot with infection. Foot Ankle **14**, 254–256 (1993)
62. E.J. Boyko, J.H. Ahroni, V.L. Stensel, D.G. Smith, D.R. Davignon, R.E. Pecoraro, Predictors of transcutaneous oxygen tension in the lower limbs of diabetic subjects. Diabet. Med. **13**, 549–554 (1996)
63. W.B. Kannel, D.L. McGee, Update on some epidemiologic features of intermittent claudication: the Framingham Study. J. Am. Geriatr. Soc. **33**(1), 13–18 (1985)
64. W.A. Marston, S.W. Davies, B. Armstrong, M.A. Farber, R.C. Mendes, J.J. Fulton et al., Natural history of limbs with arterial insufficiency and chronic ulceration treated without revascularization. J. Vasc. Surg. **44**(1), 108–114 (2006)
65. A. Karthikesalingam, P.J. Holt, P. Moxey, K.G. Jones, M.M. Thompson, R.J. Hinchliffe, A systematic review of scoring systems for diabetic foot ulcers. Diabet. Med. **27**(5), 544–549 (2010)
66. J.K. Raines, R.C. Darling, J. Buth, D.C. Brewster, W.G. Austen, Vascular laboratory criteria for the management of peripheral vascular disease of the lower extremities. Surgery **79**, 21–29 (1976)
67. R. Takolander, J.A. Rauwerda, The use of noninvasive vascular assessment in diabetic patients with foot lesions. Diabet. Med. **13**(suppl 1), S39–S42 (1995)
68. G.L. Moneta, R.A. Yeager, R.W. Lee, J.M. Porter, Noninvasive localization of arterial occlusive disease: a comparison of segmental Doppler pressures and arterial duplex mapping. J. Vasc. Surg. **17**, 578–582 (1993)
69. F.T. Padberg, T.L. Back, P.N. Thompson, R.W. Hobson II, Transcutaneous oxygen (TcPO2) estimates probability of healing in the ischemic extremity. J. Surg. Res. **60**, 365–369 (1996)
70. L. Graziani, A. Silvestro, V. Bertone, E. Manara, R. Andreini, A. Sigala, R. Mingardi, R. De Giglio, Vascular involvement in diabetic subjects with ischemic foot ulcer: a new morphologic categorization of disease severity. Eur. J. Vasc. Endovasc. Surg. **33**(4), 453–460 (2007)
71. K.A. Arsenault, J. McDonald, P.J. Devereaux, K. Thorlund, J.G. Tittley, R.P. Whitlock, The use of transcutaneous oximetry to predict complications of chronic wound healing: a systematic review and meta-analysis. Wound Repair Regen. **19**, 657–663 (2011)
72. J.L. Mills Sr, Open bypass and endoluminal therapy: complementary techniques for revascularization in diabetic patients with critical limb ischaemia. Diabetes Metab. Res. Rev. **24**(Suppl 1), S34–S39 (2008)
73. F. Pomposelli, Arterial imaging in patients with lower extremity ischemia and diabetes mellitus. J. Vasc. Surg. **52**(3 Suppl), 81S–91S (2010)
74. R. Collins, J. Burch, G. Cranny, R. Aguiar-Ibáñez, D. Craig, K. Wright, E. Berry, M. Gough, J. Kleijnen, M. Westwood, Duplex ultrasonography, magnetic resonance angiography, and computed tomography angiography for diagnosis and assessment of symptomatic, lower limb peripheral arterial disease: systematic review. BMJ **334**(7606), 1257 (2007)
75. R. Met, S. Bipat, D.A. Legemate, J.A. Reekers, M.J. Koelemay, Diagnostic performance of computed tomography angiography in peripheral arterial disease: a systematic review and meta-analysis. JAMA **301**, 415–424 (2009)
76. M.H. Heijenbrok-Kal, M.C. Kock, M.G. Hunink, Lower extremity arterial disease: multidetector CT angiography meta-analysis. Radiology **245**, 433–439 (2007)
77. D.J. Dinter, K.W. Neff, G. Visciani, R. Lachmann, C. Weiss, S.O. Schoenberg, H.J. Michaely, Peripheral bolus-chase MR angiography: analysis of risk factors for nondiagnostic image quality of the calf vessels—a combined retrospective and prospective study. AJR Am. J. Roentgenol. **193**, 234–240 (2009)
78. G. Andreisek, T. Pfammatter, K. Goepfert, D. Nanz, P. Hervo, R. Koppensteiner, D. Weishaupt, Peripheral arteries in diabetic patients: standard bolus-chase and time-resolved MR angiography. Radiology **242**, 610–620 (2007)
79. N. Diehm, A. Shang, A. Silvestro, D.D. Do, F. Dick, J. Schmidli, F. Mahler, I. Baumgartner, Association of cardiovascular risk factors with pattern of lower limb atherosclerosis in 2659 patients undergoing angioplasty. Eur. J. Vasc. Endovasc. Surg. **31**(1), 59–63 (2006)
80. A. Ndip, L. Lavery, A.J.M. Boulton, Diabetic foot disease in people with advanced nephropathy and those on renal dialysis. Curr. Diabetes Rep. **10**, 283–290 (2010)
81. M. Heikkinen, M. Salmenperä, A. Lepäntalo, M. Lepäntalo, Diabetes care for patients with peripheral arterial disease. Eur. J. Vasc. Endovasc. Surg. **33**, 583–591 (2007)
82. M.R. Prince, H. Zhang, M. Morris, J.L. MacGregor, M.E. Grossman, J. Silberzweig, R.L. DeLapaz, H.J. Lee, C.M. Magro, A.M. Valeri, Incidence of nephrogenic systemic fibrosis at two large medical centers. Radiology **248**(3), 807–816 (2008)
83. C. Rydahl, H.S. Thomsen, P. Marckmann, High prevalence of nephrogenic systemic fibrosis in chronic renal failure patients exposed to gadodiamide, a gadolinium-containing magnetic resonance contrast agent. Invest. Radiol. **43**(2), 141–144 (2008)
84. R. Wertman, E. Altun, D.R. Martin, D.G. Mitchell, J.R. Leyendecker, R.B. O'Malley, D.J. Parsons, E.R. Fuller 3rd, R.C. Semelka, Risk of nephrogenic systemic fibrosis: evaluation of gadolinium chelate contrast agents at four American universities. Radiology **248**(3), 799–806 (2008)
85. J. Apelqvist, T. Elgzyri, J. Larsson, M. Löndahl, P. Nyberg, J. Thörne, Factors related to outcome of neuroischemic/ischemic foot ulcer in diabetic patients. J. Vasc. Surg. **53**(6), 1582–1588 (2011)
86. E. Faglia, G. Clerici, J. Clerissi, L. Gabrielli, S. Losa, M. Mantero, M. Caminiti, V. Curci, A. Quarantiello, T. Lupattelli, A. Morabito, Long-term prognosis of diabetic patients with critical limb ischemia: a population-based cohort study. Diabetes Care **32**(5), 822–827 (2009)
87. L. Uccioli, R. Gandini, L. Giurato, S. Fabiano, E. Pampana, V. Spallone, E. Vainieri, G. Simonetti, Long-term outcomes of diabetic patients with critical limb ischaemia followed in a tertiary referral diabetic foot clinic. Diabetes Care **33**(5), 977–982 (2010)
88. Hinchliffe et al., A systematic review of the effectiveness of revascularization of the ulcerated foot in patients with diabetes and peripheral arterial disease. Diabetes Metab. Res. Rev. **28**(Suppl 1), 179–217 (2012)
89. E. Faglia, G. Clerici, J. Clerissi, M. Mantero, M. Caminiti, A. Quarantiello et al., When is a technically successful peripheral angioplasty effective in preventing above-the-ankle amputation in diabetic patients with critical limb ischaemia? Diabet. Med. **24**, 823–829 (2007)
90. F. Sigala, Ch. Menenakos, P. Sigalas, Ch. Baunach, S. Langer, E. Papalambros et al., Transluminal angioplasty of isolated crural arterial lesions in diabetics with critical limb ischemia. VASA **34**, 186–191 (2005)
91. T. Zeller, S. Sixt, A. Rastan, New techniques for endovascular treatment of peripheral artery disease with focus on chronic critical limb ischemia. VASA **38**, 3–12 (2009)
92. H.H. Dosluoglu, G.S. Cherr, P. Lall, L.M. Harris, M.L. Dryjski, Peroneal artery-only runoff following endovascular revascularizations is effective for limb salvage in patients with tissue loss. J. Vasc. Surg. **48**, 137–143 (2008)
93. E. Faglia, L. Dalla Paola, G. Clerici, J. Clerissi, L. Graziani, M. Fusaro, L. Gabrielli, S. Losa, A. Stella, M. Gargiulo, M.

Mantero, M. Caminiti, S. Ninkovic, V. Curci, A. Morabito, Peripheral angioplasty as the first-choice revascularization procedure in diabetic patients with critical limb ischemia: prospective study of 993 consecutive patients hospitalized and followed between 1999 and 2003. Eur. J. Vasc. Endovasc. Surg. **29**(6), 620–627 (2005)
94. L. Graziani, A. Piaggesi, Indications and clinical outcomes for below knee endovascular therapy: review article. Catheter. Cardiovasc. Interv. **75**(3), 433–443 (2010)
95. M. Manzi, M. Fusaro, T. Ceccacci, G. Erente, L. Dalla Paola, E. Brocco, Clinical results of below-the knee intervention using pedal-plantar loop technique for the revascularization of foot arteries. J. Cardiovasc. Surg. **50**(3), 331–337 (2009)
96. D.M. Ihnat, J.L. Mills Sr, Current assessment of endovascular therapy for infrainguinal arterial occlusive disease in patients with diabetes. J. Vasc. Surg. **52**(Suppl 3), 92S–95S (2010)
97. V.A. Alexandrescu, G. Hubermont, Y. Philips, B. Guillaumie, C. Ngongang, P. Vandenbossche, K. Azdad, G. Ledent, J. Horion, Selective primary angioplasty following an angiosome model of reperfusion in the treatment of Wagner 1–4 diabetic foot lesions: practice in a multidisciplinary diabetic limb service. J. Endovasc. Ther. **15**(5), 580–593 (2008)
98. C. Setacci, G. De Donato, F. Setacci, E. Chisci, Ischemic foot: definition, etiology and angiosome concept. J. Cardiovasc. Surg. **51**(2), 223–231 (2010)
99. R.F. Neville, C.E. Attinger, E.J. Bulan, I. Ducic, M. Thomassen, A.N. Sidawy, Revascularization of a specific angiosome for limb salvage: does the target artery matter? Ann. Vasc. Surg. **23**(3), 367–373 (2009)
100. C.E. Attinger, K.K. Evans, E. Bulan, P. Blume, P. Cooper, Angiosomes of the foot and ankle and clinical implications for limb salvage: reconstruction, incisions, and revascularization. Plast. Reconstr. Surg. **117**(7 Suppl), 261S–293S (2006)
101. M.I. Söderström, E.M. Arvela, M. Korhonen, K.H. Halmesmäki, A.N. Albäck, F. Biancari, M.J. Lepäntalo, M.A. Venermo, Infrapopliteal percutaneous transluminal angioplasty versus bypass surgery as first-line strategies in critical leg ischemia: a propensity score analysis. Ann. Surg. **252**(5), 765–773 (2010)
102. R. Met, K.P. Van Lienden, M.J. Koelemay, S. Bipat, D.A. Legemate, J.A. Reekers, Subintimal angioplasty for peripheral arterial occlusive disease: a systematic review. Cardiovasc. Interv. Radiol. **31**, 687–697 (2008)
103. F.B. Pomposelli, N. Kansal, A.D. Hamdan, A. Belfield, M. Sheahan, D.R. Campbell, J.J. Skillman, F.W. Logerfo, A decade of experience with dorsalis pedis artery bypass: analysis of outcome in more than 1000 cases. J. Vasc. Surg. **37**, 307–315 (2003)
104. M. Kalani, J. Apelqvist, M. Blombäck, K. Brismar, B. Eliasson, J.W. Eriksson et al., Effect of dalteparin on the healing of chronic foot ulcers in diabetic patients with peripheral arterial occlusive disease: a prospective, randomized, double-blind, placebo-controlled study. Diabetes Care **26**(9), 2575–2580 (2003)
105. M. Rullan, L. Cerda, G. Frontera, L. Masmiquel, J. Llobera, Treatment oc chronic diabetic foot ulcers with bemiparin a randomized, triple-blind, placebo controlled, clinical trial. Diabet. Med. **25**(9), 1090–1095 (2008). Erratum in: Diabet. Med. **25**(10), 1257 (2008)
106. M. Weck, H. Rietzsch, H. Lawall, U. Pichlmeier, P. Bramlage, S. Schellong, Intermittent intravenous urokinase for critical limb ischemia in diabetic foot ulceration. Thromb. Haemost. **100**(3), 475–482 (2008)
107. R.J. Hinchliffe, G.D. Valk, J. Apelqvist, D.G. Armstrong, K. Bakker, F.L. Game et al., A systematic review of the effectiveness of interventions to enhance the healing of chronic ulcers of the foot in diabetes. Diabetes Metab. Res. Rev. **24**(Suppl 1), S119–S144 (2008)
108. Game et al., A systematic review of interventions to enhance the healing of chronic ulcers of the foot in diabetes. Diabetes Metab. Res. Rev. **28**(Suppl 1), 119–141 (2012)
109. M. Eneroth, J. Larsson, J. Apelqvist, Foot infections in diabetes mellitus—entity with different characteristics, treatment and prognosis. J. Diabetes Complicat. **13**(5–6), 254–263 (1999)
110. M. Eneroth, J. Apelqvist, Clinical characteristics and outcome in diabetic patients with deep foot infections. Foot Ankle **18**, 716–722 (1997)
111. B.A. Lipsky, A.R. Berendt, J. Embil, F. de Lalla, Diagnosing and treating diabetic foot infections. Diabetes Metab. Res. Rev. **20**(Suppl 1), S56–S64 (2004)
112. L.A. Lavery, D. Armstrong, R. Wunderlich, M. Mohler, C. Wendel, B. Lipsky, Risk factors for foot infections in individuals with diabetes. Diabetes Care **29**, 1288–1293 (2006)
113. B.A. Lipsky, Y.P. Tabak, R.S. Johannes et al., Skin and soft tissue infections in hospitalised patients with diabetes: culture isolates and risk factors associated with mortality, length of stay and cost. Diabetologia **53**, 914–923 (2010)
114. A.R. Berendt, E.J. Peters, K. Bakker, J.M. Embil, M. Eneroth, R.J. Hinchliffe, W.J. Jeffcoate, B.A. Lipsky, E. Senneville, J. Teh, G.D. Valk, Diabetic foot osteomyelitis: a progress report on diagnosis and a systematic review of treatment. Diabetes Metab. Res. Rev. **24**(Suppl 1), S145–S161 (2008)
115. S. Butalia, V.A. Palda, R.J. Sargeant, A.S. Detsky, O. Mourad, Does this patient with diabetes have osteomyelitis of the lower extremity? JAMA **299**, 806–813 (2008)
116. National Institute for Health and Clinical Excellence, Diabetic foot—inpatient management of people with diabetic foot ulcers and infection (2011), http://guidance.nice.org.uk/CG119. 6/4/2011
117. G. Pellizer, M. Strazzabosco et al., Deep tissue biopsy vs superficial swap culture monitoring in the microbiological assessment of limb-threatening diabetic foot infection. Diabet. Med. **18**, 822–827 (2001)
118. D.R. Graham, C. Lucasti, O. Malafaia, R.L. Nichols, P. Holtom, N.Q. Perez, A. McAdams, G.L. Woods, T.P. Ceesay, R. Gesser, Ertapenem once daily versus piperacillin-tazobactam 4 times per day for treatment of complicated skin and skin-structure infections in adults: results of a prospective, randomized, double-blind multicenter study. Clin. Infect. Dis. **34**(11), 1460–1468 (2002)
119. N. Saltoglu, A. Dalkiran, T. Tetiker, H. Bayram, Y. Tasova, C. Dalay, M. Sert, Piperacillin/tazobactam versus imipenem/cilastatin for severe diabetic foot infections: a prospective, randomized clinical trial in a university hospital. Clin. Microbiol. Infect. **16**(8), 1252–1257 (2010)
120. D.R. Graham, D.A. Talan, R.L. Nichols, C. Lucasti, M. Corrado, N. Morgan, C.L. Fowler, Once-daily, high-dose levofloxacin versus ticarcillin-clavulanate alone or followed by amoxicillin-clavulanate for complicated skin and skin-structure infections: a randomized, open-label trial. Clin. Infect. Dis. **35**(4), 381–389 (2002)
121. B.A. Lipsky, K.J. Holroyd, M. Zasloff, Topical versus systemic antimicrobial therapy for treating mildly infected diabetic foot ulcers: a randomized, controlled, double-blinded, multicenter trial of pexiganan cream. Clin. Infect. Dis. **47**(12), 1537–1545 (2008)
122. J.S. Tan, N.M. Friedman, C. Hazelton-Miller, J.P. Flanagan, T.M. File Jr, Can aggressive treatment of diabetic foot infections reduce the need for above-ankle amputation? Clin. Infect. Dis. **23**(2), 286–291 (1996)
123. A.D. Tice, R.S. Turpin, C.T. Hoey, B.A. Lipsky, J. Wu, M.A. Abramson, Comparative costs of ertapenem and piperacillin-tazobactam in the treatment of diabetic foot infections. Am. J. Health Syst. Pharm. **64**(10), 1080–1086 (2007)

124. B.A. Lipsky, D.G. Armstrong, D.M. Citron, A.D. Tice, D.E. Morgenstern, M.A. Abramson, Ertapenem versus piperacillin/tazobactam for diabetic foot infections (SIDESTEP): prospective, randomised, controlled, double-blinded, multicentre trial. Lancet **366**(9498), 1695–1703 (2005)
125. P.G. Clay, M.R. Graham, C.C. Lindsey, K.C. Lamp, C. Freeman, A. Glaros, Clinical efficacy, tolerability, and cost savings associated with the use of open-label metronidazole plus ceftriaxone once daily compared with ticarcillin/clavulanate every 6 hours as empiric treatment for diabetic lower-extremity infections in older males. Am. J. Geriatr. Pharmacother. **2**(3), 181–189 (2004)
126. R. Lobmann, A. Ambrosch, M. Seewald, M. Dietlein, K. Zink, K.H. Kullmann, H. Lehnert, Antibiotic therapy for diabetic foot infections: comparison of cephalosporines with chinolones. Diabetes Nutr. Metab. **17**(3), 156–162 (2004)
127. R.W. Bradsher Jr, R.M. Snow, Ceftriaxone treatment of skin and soft tissue infections in a once daily regimen. Am. J. Med. **77**(4), 63–67 (1984)
128. B.A. Lipsky, U. Stoutenburgh, Daptomycin for treating infected diabetic foot ulcers: evidence from a randomized, controlled trial comparing daptomycin with vancomycin or semi-synthetic penicillins for complicated skin and skin-structure infections. J. Antimicrob. Chemother. **55**(2), 240–245 (2005)
129. G. Siami, N. Christou, I. Eiseman, K.J. Tack, Clinafloxacin versus piperacillintazobactam in treatment of patients with severe skin and soft tissue infections. Antimicrob. Agents Chemother. **45**(2), 525–531 (2001)
130. L. Harkless, J. Boghossian, R. Pollak, W. Caputo, A. Dana, S. Gray, D. Wu, An open-label, randomized study comparing efficacy and safety of intravenous piperacillin/tazobactam and ampicillin/sulbactam for infected diabetic foot ulcers. Surg. Infect. (Larchmt.) **6**(1), 27–40 (2005)
131. G.J. Noel, K. Bush, P. Bagchi, J. Ianus, R.S. Strauss, A randomized, double-blind trial comparing ceftobiprole medocaril with vancomycin plus ceftazidime for the treatment of patients with complicated skin and skin-structure infections. Clin. Infect. Dis. **46**(5), 647–655 (2008)
132. R. Vick-Fragoso, G. Hernández-Oliva, J. Cruz-Alcázar, C.F. Amábile-Cuevas, P. Arvis, P. Reimnitz, J.R. Bogner, STIC Study Group, Efficacy and safety of sequential intravenous/oral moxifloxacin vs intravenous/oral amoxicillin/clavulanate for complicated skin and skin structure infections. Infection **37**(5), 407–417 (2009)
133. B.L. Erstad, J. McIntyre, Prospective, randomized comparison of ampicillin/sulbactam and cefoxitin for diabetic foot infections. Vasc. Surg. **31**(4), 419–426 (1997)
134. B.A. Lipsky, P.D. Baker, G.C. Landon, R. Fernau, Antibiotic therapy for diabetic foot infections: comparison of two parenteral-to-oral regimens. Clin. Infect. Dis. **24**(4), 643–648 (1997)
135. B.A. Lipsky, K. Itani, C. Norden, Treating foot infections in diabetic patients: a randomized, multicenter, open-label trial of linezolid versus ampicillinsulbactam/amoxicillin-clavulanate. Clin. Infect. Dis. **38**(1), 17–24 (2004)
136. B.A. Lipsky, P. Giordano, S. Choudhri, J. Song, Treating diabetic foot infections with sequential intravenous to oral moxifloxacin compared with piperacillintazobactam/amoxicillin-clavulanate. J. Antimicrob. Chemother. **60**(2), 370–376 (2007)
137. M.L. Grayson, G.W. Gibbons, G.M. Habershaw, D.V. Freeman, F.B. Pomposelli, B.I. Rosenblum, E. Levin, A.W. Karchmer, Use of ampicillin/sulbactam versus imipenem/cilastatin in the treatment of limb-threatening foot infections in diabetic patients. Clin. Infect. Dis. **18**(5), 683–693 (1994)
138. Dutch Cochrane Centre (2011), http://www.cochrane.nl/. 8/4/2011
139. A. Yönem, B. Cakir, S. Guler, O.O. Azal, A. Corakci, Effects of granulocyte-colony stimulating factor in the treatment of diabetic foot infection. Diabetes Obes. Metab. **3**(5), 332–337 (2001)
140. F. de Lalla, G. Pellizzer, M. Strazzabosco, Z. Martini, J.G. Du, L. Lora, P. Fabris, P. Benedetti, G. Erle, Randomized prospective controlled trial of recombinant granulocyte colony-stimulating factor as adjunctive therapy for limbthreatening diabetic foot infection. Antimicrob. Agents Chemother. **45**(4), 1094–1098 (2001)
141. T. Kästenbauer, B. Hornlein, G. Sokol, K. Irsigler, Evaluation of granulocytecolony stimulating factor (Filgrastim) in infected diabetic foot ulcers. Diabetologia **46**(1), 27–30 (2003)
142. A. Gough, M. Clapperton, N. Rolando, A.V. Foster, J. Philpott-Howard, M.E. Edmonds, Randomised placebo-controlled trial of granulocyte-colony stimulating factor in diabetic foot infection. Lancet **350**(9081), 855–859 (1997)
143. M. Cruciani, B.A. Lipsky, C. Mengoli, F. de Lalla, Granulocyte-colony stimulating factors as adjunctive therapy for diabetic foot infections. Cochrane Database Syst. Rev. **8**(3), CD006810 (2009)
144. E. Faglia, G. Clerici, M. Caminiti, A. Quarantiello, M. Gino, A. Morabito, The role of early surgical debridement and revascularization in patients with diabetes and deep foot space abscess: retrospective review of 106 patients with diabetes. J. Foot Ankle Surg. **45**(4), 220–226 (2006)
145. E. Senneville, A. Lombart, E. Beltrand, M. Valette, L. Legout, M. Cazaubiel, Y. Yazdanpanah, P. Fontaine, Outcome of diabetic foot osteomyelitis treated nonsurgically: a retrospective cohort study. Diabetes Care **31**(4), 637–642 (2008)
146. K.Z. Vardakas, M. Horianopoulou, M.E. Falagas, Factors associated with treatment failure in patients diabetic foot infections: an analysis of data from randomised controlled trials. Diabetes Res. Clin. Pract. **80**, 344–351 (2008)
147. M.G. Sheahan, A.D. Hamdan, J.R. Veraldi, C.S. McArthur, J.J. Skillman, D.R. Campbell et al., Lower extremity minor amputations: the roles of diabetes mellitus and timing of revascularization. J. Vasc. Surg. **42**, 476–480 (2005)
148. P.A. Stone, M.R. Back, P.A. Armstrong, S.K. Flaherty, W.B. Keeling, B.L. Johnson, M.L. Shames, D.F. Bandyk, Midfoot amputations expand limb salvage rates for diabetic foot infections. Ann. Vasc. Surg. **19**(6), 805–811 (2005)
149. W.J. Jeffcoate, S.Y. Chipchase, P. Ince, F.L. Game, Assessing the outcome of the management of diabetic foot ulcers using ulcer-related and person-related measures. Diabetes Care **29**, 1784–1787 (2006)
150. M.J. Young, J.E. McCardle, L.E. Randall, J.I. Barclay, Improved survival of diabetic foot ulcer patients 1995–2008: possible impact of aggressive cardiovascular risk management. Diabetes Care **31**, 2143–2147 (2008)
151. J. Edwards, S. Stapley, Debridement of diabetic foot ulcers. Cochrane Database Syst. Rev. (1), CD003556 (2010). doi: 10.1002/14651858
152. F. Game, The advantages and disadvantages of non-surgical management of the diabetic foot. Diabetes Metab. Res. Rev. **24**(Suppl 1), S72–S75 (2008)
153. R. Sibbald, K. Woo, The biology of chronic foot ulcers in persons with diabetes. Diabetes Metab. Res. Rev. **24**(Suppl 1), S25–S30 (2008)
154. S.M. Bergin, P. Wraight, Silver based wound dressings and topical agents for treating diabetic foot ulcers. Cochrane Database Syst. Rev. (1), CD005082 (2006)
155. D.G. Armstrong, Diabetic Foot Study Consortium, Negative pressure wound therapy after partial diabetic foot amputation: a multicentre, randomised controlled trial. Lancet **366**, 1704–1710 (2005)
156. M.T. Eginton, K.R. Brown, G.R. Seabrook, J.B. Towne, R.A. Cambria, A prospective randomized evaluation of negative-

pressure wound dressings for diabetic foot wounds. Ann. Vasc. Surg. **17**, 645–649 (2003)
157. A. Etöz, Y. Özgenel, M. Özcan, The use of negative pressure wound therapy on diabetic foot ulcers: a preliminary controlled trial. Wounds **16**, 264–269 (2004)
158. S.K. McCallon, C.A. Knight, J.P. Valiulus, M.W. Cunningham, J.M. McCulloch, L.P. Farinas, Vacuum-assisted closure versus saline-moistened gauze in the healing of postoperative diabetic foot wounds. Ostomy Wound Manage. **46**, 28–34 (2000)
159. P.A. Blume, J. Walters, W. Payne, J. Ayala, J. Lantis, Comparison of negative pressure wound therapy using vacuum-assisted closure with advanced moist wound therapy in the treatment of diabetic foot ulcers. Diabetes Care **31**, 631–636 (2008)
160. P. Vikatmaa, V. Juutilainen, P. Kuukasjärvi, A. Malmivaara, Negative pressure wound therapy: a systematic review on effectiveness and safety. Eur. J. Vasc. Endovasc. Surg. **36**, 438–448 (2008)
161. E. Faglia, F. Favales, A. Aldeghi, P. Calia, A. Quarantiello, G. Oriani et al., Adjunctive systemic hyperbaric oxygen therapy in treatment of severe prevalently ischemic diabetic foot ulcer. A randomized study. Diabetes Care **19**, 1338–1343 (1996)
162. A. Abidia, G. Laden, G. Kuhan, B.F. Johnson, A.R. Wilkinson, P.M. Renwick et al., The role of hyperbaric oxygen therapy in ischaemic diabetic lower extremity ulcers: a double-blind randomised-controlled trial. Eur. J. Vasc. Endovasc. Surg. **25**, 513–518 (2003)
163. N. Doctor, S. Pandya, A. Supe, Hyperbaric oxygen therapy in diabetic foot. J. Postgrad. Med. **38**, 112–114 (1992)
164. G. Baroni, T. Porro, E. Faglia, G. Pizzi, A. Mastropasqua, G. Oriani et al., Hyperbaric oxygen in diabetic gangrene treatment. Diabetes Care **10**, 81–86 (1987)
165. W.A. Zamboni, H.P. Wong, L.L. Stephenson, M.A. Pfeifer, Evaluation of hyperbaric oxygen for diabetic wounds: a prospective study. Undersea Hyperb. Med. **24**, 175–179 (1997)
166. M. Kalani, G. Jörneskog, N. Naderi, F. Lind, K. Brismar, Hyperbaric oxygen (HBO) therapy in treatment of diabetic foot ulcers. Long-term follow-up. J. Diabetes Complicat. **16**, 153–158 (2002)
167. M. Löndahl, P. Katzman, A. Nilsson, C. Hammarlund, Hyperbaric oxygen therapy facilitates healing of chronic foot ulcers in patients with diabetes. Diabetes Care **33**, 998–1003 (2010)
168. T. Tan, E.J. Shaw, F. Siddiqui, P. Kandaswamy, P.W. Barry, Guideline Development Group, Inpatient management of diabetic foot problems: summary of NICE guidance. BMJ **342**, 702–703 (2011)
169. R. van Deursen, Footwear for the neuropathic patient: offloading and stability. Diabetes Metab. Res. Rev. **24**(Suppl 1), S96–S100 (2008)
170. S.A. Bus, G.D. Valk, R.W. van Deursen, D.G. Armstrong, C. Caravaggi, P. Hlavácek et al., The effectiveness of footwear and offloading interventions to prevent and heal foot ulcers and reduce plantar pressure in diabetes: a systematic review. Diabetes Metab. Res. Rev. **24**(Suppl 1), S162–S180 (2008)
171. P.R. Cavanagh, S.A. Bus, Off-loading the diabetic foot for ulcer prevention and healing. J. Vasc. Surg. **52**(3 Suppl), 37S–43S (2010)
172. T.M. Owings, J. Apelqvist, A. Stenström, M. Becker, S. Bus, A. Kalpen, J.S. Ulbrecht, P. Cavanagh, Plantar pressures in diabetic foot ulcer patients who have remained healed. Diabet. Med. **26**(11), 1141–1146 (2009)
173. I.A. Katz, A. Harlan, B. Miranda-Palma, L. Prieto-Sanchez, D.G. Armstrong, J.H. Bowker et al., A randomized trial of two irremovable off-loading devices in the management of plantar neuropathic diabetic foot ulcers. Diabetes Care **28**, 555–559 (2005)
174. D.G. Armstrong, L.A. Lavery, S. Wu, A.J. Boulton, Evaluation of removable and irremovable cast walkers in the healing of diabetic foot wounds: a randomized controlled trial. Diabetes Care **28**, 551–554 (2005)
175. P.A. Blume, L.K. Paragas, B.E. Sumpio, C.E. Attinger, Single-stage surgical treatment of noninfected diabetic foot ulcers. Plast. Reconstr. Surg. **109**, 601–609 (2002)
176. C.E. Attinger, I. Ducic, P. Cooper, C.M. Zelen, The role of intrinsic muscle flaps of the foot for bone coverage in foot and ankle defects in diabetic and nondiabetic patients. Plast. Reconstr. Surg. **110**, 1047–1054 (2002)
177. A. Piaggesi, E. Schipani, F. Campi, M. Romanelli, F. Baccetti, C. Arvia et al., Conservative surgical approach versus non-surgical management for diabetic neuropathic foot ulcers: a randomized trial. Diabet. Med. **15**, 412–417 (1998)
178. E.J. Fitzgerald O'Connor, M. Vesely, P.J. Holt, K.G. Jones, M.M. Thompson, R.J. Hinchliffe, A systematic review of free tissue transfer in the management of non-traumatic lower extremity wounds in patients with diabetes. Eur. J. Vasc. Endovasc. Surg. **41**(3), 391–399 (2011)
179. E. Tukiainen, M. Kallio, M. Lepantalo, Advanced leg salvage of the critically ischemic leg with major tissue loss by vascular and plastic surgeon teamwork: long-term outcome. Ann. Surg. **244**, 949–957 (2006)
180. C. Randon, F. Vermassen, B. Jacobs, F. De Ryck, K. Van Landuyt, Y. Taes, Outcome of arterial reconstruction and free-flap coverage in diabetic foot ulcers: long-term results. World J. Surg. **34**(1), 177–184 (2010)
181. M.J. Mueller, D.R. Sinacore, M.K. Hastings, M.J. Strube, J.E. Johnson, Effect of Achilles tendon lengthening on neuropatic plantar ulcers. A randomized clinical trial. J. Bone Joint Surg. Am. **85A**, 1436–1445 (2003)
182. N.L. Petrova, M.E. Edmonds, Charcot neuro-osteoarthropathy—current standards. Diabetes Metab. Res. Rev. **24**(Suppl 1), S58–S61 (2008)
183. H. Svensson, J. Larsson, J. Apelqvist, M. Eneroth, Minor amputations successful in patients with diabetes mellitus and severe foot ulcers threatening the survival of the foot. J. Wound Care **20**, 261-2, 264, 266 (2011)
184. V. Dargis, O. Pantelejeva, A. Jonushaite, A. Boulton, I. Vileikyte, Benefits of a multidisciplinary approach in the management of recurrent diabetic foot ulceration in Lithuania: a prospective study. Diabetes Care **22**(9), 1428–1431 (1999)
185. C.J. McCabe, R.C. Stevenson, A.M. Dolan, Evaluation of diabetic foot screening and protection programme. Diabetes Med. **15**, 80–84 (1998)
186. J. Larsson, C.D. Agardh, J. Apelqvist, A. Stenström, Long term prognosis after amputation in diabetic patients. Clin. Orthop. Relat. Res. **350**, 149–158 (1998)