HIPPOKRATIA 2009, 13, 4: 199-204

INVITED ARTICLE

The Diabetic foot: A global threat and a huge challenge for Greece

Papanas N, Maltezos E

Outpatient Clinic of the Diabetic Foot, 2nd Department of Internal Medicine, Democritus University, Thrace, Greece

Abstract

The diabetic foot continues to be a major cause of morbidity, posing a global threat. Substantial progress has been now accomplished in the treatment of foot lesions, but further improvement is required. Treatment options may be classified into established measures (revascularisation, casting and debridement) and new modalities. All therapeutic measures should be provided by specialised dedicated multidisciplinary foot clinics. In particular, the diabetic foot is a huge challenge for Greece. There is a dramatic need to increase the number of engaged foot care teams and their resources throughout the country. It is also desirable to continue education of both physicians and general diabetic population on the magnitude of the problem and on the suitable preventative measures. At the same time, more data on the prevalence and clinical manifestations of the diabetic foot in Greece should be carefully collected. Finally, additional research should investigate feasible ways of implementing current knowledge in everyday clinical practice. Hippokratia 2009; 13 (4): 199-204

Key words: amputations; diabetes mellitus; diabetic foot; diabetic neuropathy; peripheral arterial disease; ulceration

Corresponding author: Papanas N, Dpt of Internal Medicine, Democritus University of Thrace, 22 G. Kondyli Street, Alexandroupolis, Greece, Tel: +30 6977 544337, Fax: +30 25510 74723, Email: papanasnikos@yahoo.gr

The diabetic foot was recognised in the 19th century, but it was only in the second half of the 20th century that scientists and clinicians paid due attention to the magnitude of the problem[1,2]. It is now understood that the diabetic foot represents one of the major chronic complications of diabetes, posing a tremendous impact on morbidity and mortality of the diabetic population[2-5]. In 2005, it was estimated that a lower limb was lost every 30 seconds due to diabetes in some part of the world[3]. Overall, one out of four patients with diabetes runs the risk of sustaining a foot lesion throughout his/her lifetime[6]. Worldwide, the prevalence of the diabetic foot ranges between 1.4% and 5.9%[2]. Foot ulceration and amputation are significantly inter-related in diabetes[2,3]. Indeed, more than 85% of amputations resulted from a previous ulcer[2]. Importantly, diabetes is the foremost cause of non-traumatic lower extremity amputation in the Western world, amputation rates among diabetic patients being 15 times higher than in the non-diabetic subjects[2,3].

This review briefly outlines the global threat of the diabetic foot with particular emphasis on the situation in Greece.

Main aspects of pathophysiology

Three major pathologies, mutually interacting, result in the diabetic foot: ischaemia, neuropathy and infection[1,2,5,7]. Ischaemia was recognised in the 19th century as a manifestation of peripheral arterial disease (PAD), which is more common in diabetes, and affects multiple vessels, with a predilection for the infra-popliteal arteries (anterior tibial, posterior tibial and peroneal artery)[3,5,7,8]. Initially, PAD may be silent, and so diabetic patients may present late with severe peripheral tissue hypoxia threatening limb viability, especially in the face of superimposed infection[3,7]. Generally, prognosis of PAD is worse in patients with diabetes[3,5,7,8].

The role of neuropathy was only appreciated in the second half of the 20th century[1,2]. Neuropathy is responsible for stocking-distribution sensory loss: the feet lose sensation of noxious stimuli, such as trauma induced by stepping on a sharp object or skin injury due to ill-fitting shoes[9-12]. Initially, foot injury may be trivial, but remain unperceived, eventually leading to progressing deep tissue destruction[9-12]. Moreover, intrinsic foot muscles are deprived of normal innervation. Loss of innervation may result in muscle atrophy and foot deformities, mostly prominent metatarsal heads and claw or hammer toes[9-13]. Thus, pressures are gradually abnormally distributed on the plantar aspect of the foot, in a way that some plantar sites have very high pressures and become prone to ulceration[9-13]. Impaired pressure distribution is aggravated by limited joint mobility (LJM). LJM is a generalised phenomenon in diabetes, mediated by increased non-enzymatic collagen glycosylation in the peri-articular tissues. In the foot, it mainly affects the fist metatarsophalangeal joint and contributes to elevated plantar pressure at the first metatarsal head[13]. Of note, a rather frequently underestimated manifestation of neuropathy is reduced sweating, alternatively called sudomotor impairment[14]. This is responsible for dry skin and callus formation. Skin fissures may become gates of entry for bacteria and increase the likelihood of infection[14].

Ischaemia and neuropathy predispose to infection[13,15,16]. The vast majority of chronic foot ulcers become infected[13]. In acute infections, gram-positive cocci predominate. In chronic cases, though, infection is multimicrobial by gram-positive cocci, gram-negative bacteria and anaerobes[13,15,16]. Methicillin-resistant Staphylococcus aureus (MRSA) is becoming a nightmare for diabetic foot clinics[17]. An important diagnostic pitfall is the paucity of symptoms and signs. Indeed, tissue immune response to infection is hampered by ischaemia and neuropathy[13]. To the inexperienced eye, the foot may appear normal and antibiotic treatment may be unduly delayed[13,15,16]. Infection may even extend to ligaments, tendons and bones, compromising survival of both limb and patient[13,15,16]. For this reason, it is vital to diagnose infection early and assess its severity, as well as vascular status and comorbid conditions[13,15,16]. In the expert setting, depth of a foot lesion, the presence and extent of infection, the evidence of bony involvement and the presence or otherwise of ischaemia are carefully assessed by detailed evaluation systems (Wagner classification, University of Texas classification, International Working Group on the Diabetic Foot classification)[9,15,16]. In general practice, it is, probably, more convenient to distinguish between limb-threatening and not limb-threatening infections[13]. In the latter, presenting features include: cellulitis > 2cm; oedema, pain or lymphangitis; drainage or foul odour; infection extending to the bone or joint; systemic signs and symptoms; severe ischaemia[13].

Main aspects of treatment

Treatment modalities of the diabetic foot may be divided into established and emerging ones, as reviewed in more detail elsewhere[13]. Established treatment addresses the three major aetiologic factors discussed above. It attempts to restore blood flow to the limb, off-load high-pressure areas and tackle infection[9,13,15,16].

Restoration of blood flow is called revascularisation or arterial reconstruction[13]. This is achieved either by the open surgical approach (by-pass graft surgery) or by endovascular techniques (percutaneous transluminal angioplasty, PTA)[18-21]. Both modalities have proved effective in restoring adequate arterial perfusion among diabetic patients[18-21]. Indeed, they significantly increase limb survival rates and have dramatically improved outcomes in the diabetic foot[2,13,18-21]. They may also be reliably used to improve blood flow in the setting of critical limb ischaemia[13,18-19]. An additional advantage of PTA is that it can easily be repeated in the same patient in case of restenosis[13,18,19]. However, the choice of revascularisation technique is for the expert to decide. The final choice of procedure depends on the anatomic site and extent of the ischaemic lesion, the surgeon's experience and the patient's comorbidities[13,18-20].

In neuropathic foot ulcers with adequate arterial perfusion, it is important to reduce mechanical stress at the site of the ulcer[7, 13,22,23]. Pressure relief is achieved by off-loading techniques involving the application of some form of cast. The "golden standard" in off-loading techniques is the Total Contact Cast (TCC), an irremovable cast made of stockinette, low-density foam, elastic plaster and fibreglass, with a rockerbottom sole[7,11,13,22]. A useful variant is "instant Total Contact Cast", a simple cast walker made irremovable by a layer of cohesive bandage[23]. This "instant Total Contact Cast" is much simpler to make and does not call for experienced personnel. Removable cast walkers include the Scotch cast boot (a removable boot of stockinette, felt and fibreglass tape) and the Aircast walker (a cast with four air cells that is inflated by a hand pump)[7,11,13,22]. To decrease weight-bearing, casting should be combined with patient immobilisation, as well as use of crutches and wheelchairs[7,11,13].

Pressure relief can be improved by removal of callus and necrotic tissue that increase mechanical stress and impede proper healing[13,15,24,25]. Removal of non-viable material, foreign bodies, and poorly healing tissue from a wound is called debridement and is, typically, performed surgically by means of a scalpel[13,15,24,25]. Debridement aims to diminish plantar pressure by taking away excessive callus, to remove necrotic tissue, bacteria and any foreign bodies, to promote drainage of exudate and to facilitate healthy granulation[13,15,24,25]. An additional advantage is that it reveals true ulcer depth and permits obtaining a deep tissue specimen for culture[13,15,24]. Alternatively, the foot may be debrided by non-surgical modes[13,25]. These include autolytic, enzymatic, mechanical and biological debridement. Such methods of debridement represent viable solutions for patients at high risk for surgery and for foot care teams with poor access to a surgeon[13,25]. Enzymatic debridement by use of enzymatic agents (papain or collagenase) and mechanical debridement by application of a saline-moistened gauze to the wound, which is removed without wetting once it gets dry, are the most practical ways of debridement[13,25]. Biological debridement by application of sterile maggots that selectively remove necrotic tissue is considered the most promising non-surgical mode of debridement[13,25]. All debridement options can be used in combination with a vacuum-assisted closure (VAC) pump. This device applies negative pressure to the ulcer and has been shown to improve the rates of granulation tissue formation and wound healing[26].

Management of infection is of vital importance. Antibiotics should be prescribed without delay when there is clinical suspicion of infection, such as pain, erythema, discolouration or friable granulation tissue[7,13,15,16]. Clinical presentation does not reveal the species of bacteria. As a general rule, though, the initial regimen should definitely cover Staphylococcus and other gram-positive cocci[7,13-16]. The likelihood of gram-negative bacteria and/or anaerobes is increased in the face of necrosis[7, 13,15]. In practice, broad-spectrum antibiotics are initially required, and, at the same time, tissue or a deep-wound swab should be sent for culture. Culture results will help adjusting the

initial antibiotic regimen[13,15,16]. Further treatment plan differs according to the type of infection, i.e. limb-threatening vs. not limb-threatening[13,15,16]. The former may be treated by oral or parenteral antibiotics, while the latter necessitates intravenous therapy[13,15,16]. Indeed, patients with limb-threatening infections need prompt hospitalisation for intravenous antibiotic administration and meticulous monitoring[13,15,16]. Adjuvant foot surgery (surgical debridement of all necrotic tissue, drainage of abscess, open wound management, resection of osteomyelitic bone, foot-sparing reconstructive procedures and even amputation) is often required[9,13,15]. Naturally, urgent revascularisation should be performed in all cases of severe ischaemia[9,13,15,20].

The choice of the antibiotic regimen depends both on severity of infection and on local prevalence of micro-organisms and their sensitivities[13,15,16]. In not limb-threatening infections, amoxycyllin/clavulanate or 2nd generation cephalosporins are generally sufficient. In case of recent β-lactam antibiotic administration, one may also consider fluoroquinolones (ofloxacin or ciprofloxacin) and in case of allergy to β-lactam antibiotics, clindamycin, trimethoprim/sulfamethoxazole or fluoroquinolones may be administered[13,15,16]. In limb-threatening infections, carbapenems (imipenem/cilastatin or meropenem), 3rd or 4th generation cephalosporins, fluoroquinolone+clindamycin or clindamycin+aminoglycoside should be prescribed. Glycopeptides (vancomycin or teicoplanin) or linezolid may be added in case of suspected MRSA[9,13,15,16]. Nelson et al have reviewed available evidence, finding that no particular antimicrobial agent can be put forward as ideal and that large studies on the effectiveness and cost-effectiveness of antimicrobial interventions are needed[27]. More recently, linezolid, ertapenem and Piperacillin/Tazobactam have been approved by the FDA for diabetic foot infections[28].

Emerging treatment options include: a) topical use of growth factors (mainly Platelet-derived Growth Factor, PDGF), b) pharmacological induction of new vessels by administration of various growth factors (therapeutic angiogenesis), c) various bioengineered skin substitutes and extracellular matrix proteins, d) hyperbaric oxygen, e) additional miscellaneous topical treatments[13,29-31]. Such therapeutic measures should be implemented either in combination with established treatments or after established treatments failed[13,31].

Prevention

Prevention of the diabetic foot can be divided into primary and secondary[3]. Primary prevention is designed for the general diabetic population and aims to avert ulcerous lesions. Secondary prevention addresses subjects with prior ulceration and/or amputation. It focuses on prevention of relapse and of further amputation in the ipsilateral or contralateral limb[3]. Education is the cornerstone of both primary and secondary prevention[3,32,33]. Education increases physician and public awareness of diabetic foot lesions and conveys knowledge on foot hygiene, daily self-examination and preventative measures to reduce relapse of ulceration[3,32,33]. Education is especially useful in elderly people or patients with end-stage renal disease, in whom diabetic foot lesions occur more frequently and carry a more sinister prognosis[3,34]. Other prophylactic measures include regular podiatric screening and appropriate footwear. Podiatric screening offers the opportunity of diagnosing any presenting condition early enough and of correcting high-risk factors, such as callus, onychomycoses, ingrown toenails and toe deformities[3,13]. Proper shoes should be spacious enough, especially for the toes, and their heels should not be too high[3,13]. More severe cases, notably profound foot deformities, call for specially designed bespoke shoes with extra depth and accommodating insoles[3,13]. Of note, the ideal setting to provide education and prevention is the multidisciplinary foot clinic, because this approach is the only way of achieving better foot care and reducing amputation rates[35-37].

The diabetic foot: a huge challenge for Greece

The diabetic foot is also an important medical issue in Greece. To the best of our knowledge, there is little data on its frequency and management. The prevalence of diabetic foot lesions has been reported to be 4.75%[38]. More than half of patients with diabetic foot have at least one risk factor, mainly neuropathy and vascular disease[38]. Doupis et al have studied 742 consecutive patients with type 2 diabetes and compared those with foot ulcer (n= 234) to those without (n= 508)[39]. The former had, in comparison to the latter, significantly longer diabetes duration (median duration: 19 vs. 10 years, $p< 0.001$), significantly lower Body Mass Index (27.9±5.5 kg/m^2 vs. 28.9±5.6 kg/m^2, $p= 0.03$), significantly lower creatinine clearance (65.9±28.2 ml/min vs. 77.9±38.0 ml/min, $p= 0.003$), significantly higher frequency of coronary artery disease (29.5% vs. 20.1%, $p= 0.005$) and PAD (27.8% vs. 7.7%, $p< 0.001$), as well as significantly higher frequency of retinopathy (35.0% vs. 18.9%, $p< 0.001$) and nephropathy (16.7% vs. 11.4%, $p= 0.04$)[39].

Similarly, little is known on the aetiology of diabetic foot ulceration. In the study by Doupis et al, the majority of diabetic foot patients had neuropathic (64.9%) rather than neuroischaemic ulcer (35.1%)[39]. In another specialised centre, 52.3% of patients had neuropathic, 36.0% had neuroischaemic and 11.7% ischaemic ulcers (Vogiatzoglou D, personal communication). By contrast, Skoutas et al have reported 52.1% frequency of neuroischaemic, 17.9% frequency of ischaemic and 30% frequency of neuropathic ulceration[40]. These authors believe that the frequency of the neuroischaemic foot is rising, but such increase has not, at the moment, been confirmed throughout Greece. Interestingly, there is evidence to suggest that neuroischaemic patients have different clinical characteristics from neuropathic patients[39]. Specifically, age was significantly higher in neuroischaemic than in neuro-

pathic patients (67.4±10.6 years vs. 64.0±12.6 years, p= 0.04) and the same held true for diabetes duration (median duration: 19 years vs. 13 years, p= 0.001)[39]. Neuroischaemic patients had significantly higher frequency of smoking (51.2% vs. 18.4%, p= 0.001), hypertension (73.1% vs. 47.3%, p< 0.001), dyslipidaemia (60.9% vs. 34.2%, p= 0.001), retinopathy (56% vs. 23.6%, p< 0.001), nephropathy (32.9% vs. 7.9%, p<0.0001) and coronary artery disease (53.6% vs. 16.4%, p< 0.001)[39]. Ankle-Brachial Index and creatinine clearance were significantly higher in neuropathic patients (p< 0.001 and p= 0.01, respectively)[39]. Finally, 75.6% of neuroischaemic patients and only 52.6% of neuropathic patients were male (significant difference at p= 0.001)[39]. Of note, PAD in diabetic patients with coronary ischaemia is also a moderately accurate predictor of the extent of coronary atherosclerosis (52.38% sensitivity and 69.80% specificity for the diagnosis of angiographically severe coronary artery disease)[40,41].

Infection is also common in diabetic foot ulceration. In particular, MRSA (Methicillin-resistant Stapylococcus aureus) is a growing concern[42]. The prevalence of MRSA was found significantly higher in patients with infected foot ulcers and MRSA infection or colonisation was not associated with known risk factors. This high prevalence of MRSA in patients with foot ulcers may reflect the increased prevalence of MRSA in the community[42].

Data on the frequency of amputations is also sparse. In a population study, Karagianni found that the prevalence of amputations in 1999 was 12.5/1000 patients, equivalent to 2.48/10000 general population[43]. Mean 10-year incidence of amputations (1990-1999) was 3.7/1000 patients per year, equivalent to 0.59/10000 general population per year[43]. There was a male preponderance among amputees, and mortality was as high as 56%, three times higher than the general population[43]. The level of amputation was as follows: above knee 18%, below knee 18%, foot 29% and toe 35%[43]. Of all amputations, 47% were performed in the right and 38% in the left lower limb, while 15% were bilateral[43]. In another survey, diabetic patients underwent a second amputation (p= 0.003) and a contralateral amputation (p= 0.02) significantly more frequently than non-diabetic subjects. Predictors of all-cause mortality in the diabetic group, after adjustment for sex, were age (hazard ratio: 1.04 (1.02-1.06); p< 0.001) and the level of amputation (major vs. minor) (hazard ratio: 1.55, p= 0.05)[44]. Skoutas et al examined the re-amputation rates and risk factors for ipsilateral re-amputation in patients with diabetic foot and prior amputation[40]. Re-amputation was required in 21.5% of patients during a mean follow-up of 18 months and most re-amputations were performed within the first 6 months of the initial amputation[40]. On multivariate analysis, age (hazard ratio 1.06 by increase of 1 year) and heel lesions (hazard ratio 2.69) were significantly associated with ipsilateral re-amputation[40].

Management of the diabetic foot is quite variable in Greece. Regrettably, there is neither a reliable database nor a national treatment algorithm. Clearly, therapeutic strategy differs between specialised multi-disciplinary foot clinics and small local hospitals. In 1999, Staramos et al reported that femoro-distal by-pass graft surgery, and vascular re-construction in general, was underused in Greece[45]. Since then, considerable progress seems to have been made, and the number of vascular procedures appears to have increased, at least in the large cities. However, an objective record of this progress is still eagerly awaited.

Implications for improved foot care in Greece

During the last five years, there is an improvement in the study of the diabetic foot in Greece. Indeed, some authors have investigated epidemiology[38,39,41-44], while others have studied new diagnostic tests[46,51] and clinical manifestations of neuropathy[38,52-55], as well as diagnosis of PAD[56]. Importantly, the Hellenic Association for the Study of the Diabetic Foot was established in 2005, and the Hellenic Diabetes Association created the Study Group of Neuropathy and the Diabetic Foot in the following year. Thanks to these associations, numerous scientific meetings on the diabetic foot have been held throughout Greece.

What, then, should be the next step? In the authors' opinion, the need for progress may be outlined as follows:

a) Collection of more data on the prevalence and clinical manifestations of the diabetic foot in Greece

b) Continued education of both physicians and general diabetic population

c) Improvement of organised multidisciplinary foot care throughout the country

d) Formulation of a national treatment algorithm

e) Continuous research

Continuous research might shed more light on the following issues:

a) Frequency of amputations and potential geographical differences

b) Current situation of microbial flora in the diabetic foot and assessment of resistance to antibiotics

c) Utilisation of new diagnostic tests for neuropathy in clinical practice

d) Utilisation of new imaging modalities in clinical practice

e) Current use of revascularisation and room for improvement

f) Current use of off-loading techniques and ways of improvement

g) Improved use of therapeutic adjuncts (hyperbaric oxygen, growth factors etc) in everyday situations

Conclusions

The diabetic foot is a global threat, because it continues to be a major cause of morbidity and mortality[2,3,5,7]. Although significant progress has been achieved over the

past years, there is still a vital need for further improvement. At present, revascularisation, casting and debridement remain the established therapeutic modalities and constitute the cornerstone of management[9,13,15,16]. New treatments are also being developed and hold promise for the near future[13,31]. All forms of treatment need to be provided by a dedicated multidisciplinary foot care team, in order to reduce amputation rates[35-37].

In particular, the diabetic foot is a huge challenge for Greece. Some improvement has been achieved during the last years, but there is still very long way to go. The most important necessity is the improvement of organised multidisciplinary foot care throughout the country. There is a dramatic need to increase the number of engaged foot care teams and their resources. It is also desirable to continue education of both physicians and general diabetic population on the magnitude of the problem and on the suitable preventative measures. At the same time, more data on the prevalence and clinical manifestations of the diabetic foot in Greece should be carefully collected. Finally, additional research should explore ways of implementing current knowledge (choice of antibiotics, imaging modalities, improved off-loading) in everyday clinical practice.

References

1. Connor H. Some historical aspects of diabetic foot disease. Diabetes Metab Res Rev. 2008; 24 (Suppl 1): S7-S13.
2. Boulton AJM. The diabetic foot: grand overview, epidemiology and pathogenesis. Diabetes Metab Res Rev. 2008; 24 (Suppl 1): S3-S6.
3. Bakker K, Foster AVM, van Houtoum WH, Riley P (Eds). International Diabetes Federation and International Working Group of the Diabetic Foot. Time to act. The Netherlands. 2005.
4. van Houtum W. Barriers to the delivery of diabetic foot care. Lancet. 2005; 366: 1678-1679.
5. Papanas N, Maltezos E, Edmonds M. St. Vincent declaration after 15 years or who cleft the devil's foot? Vasa. 2006; 35: 3-4.
6. Reiber GE, Ledoux WR. Epidemiology of diabetic foot ulcers and complications: evidence for prevention. In: Williams R, Herman W, Kinmoth AL, Wareham NJ (Eds): the evidence base for diabetes care. Chichester: Wiley. 2002; 641-665.
7. Edmonds M. The diabetic foot, 2003. Diabetes Metab Res Rev. 2004; 20 (Suppl 1): S9-S12.
8. Jude EB, Oyibo SO, Chalmers N, Boulton AJ. Peripheral arterial disease in diabetic and nondiabetic patients: a comparison of severity and outcome. Diabetes Care. 2001; 24: 1433-1437.
9. Frykberg RG, Zgonis T, Armstrong DG, Driver VR, Giurini JM, Kravitz SR, et al. Diabetic foot disorders: A clinical practice guideline (2006 revision). J Foot Ankle Surg. 2006; 45 (Suppl 1): S1-S66.
10. Boulton AJ, Kirsner RS, Vileikyte L. Clinical practice. Neuropathic diabetic foot ulcers. N Engl J Med. 2004; 351: 48-55.
11. Edmonds ME, Foster AVM, Sanders LJ. Stage 3: the ulcerated foot. In: Edmonds ME, Foster AVM, Sanders LJ, A Practical Manual of diabetic footcare, Oxford: Blackwell. 2004, 62-101.
12. Veves A, Manes C, Murray HJ, Young MJ, Boulton AJ. Painful neuropathy and foot ulceration in diabetic patients. Diabetes Care. 1993; 16: 1187-1189.
13. Papanas N, Maltezos E. The diabetic foot: established and emerging treatments. Acta Clin Belg. 2007; 62: 230-238.
14. Tentolouris N, Marinou K, Kokotis P, Karanti A, Diakoumopoulou E, Katsilambros N. Sudomotor dysfunction is associated with foot ulceration in diabetes. Diabet Med. 2009; 26: 302-305.
15. Edmonds ME, Foster AVM, Sanders LJ. Stage 4: the infected foot. In: Edmonds ME, Foster AVM, Sanders LJ, A Practical Manual of diabetic footcare, Oxford: Blackwell. 2004, 102-140.
16. Lipsky BA, Berendt AR, Deery HG, et al. Diagnosis and treatment of diabetic foot infections. Plast Reconstr Surg. 2006; 117(7 Suppl): 212S-238S.
17. Dang CN, Prasad YD, Boulton AJ, Jude EB. Methicillin-resistant Staphylococcus aureus: a worsening problem. Diabet Med. 2003; 20: 159-161.
18. Sigala F, Georgopoulos S, Langer S, Baunach C, Papalambros E, Sigalas K, et al. Outcome of infrainguinal revascularization for critical limb ischemia in diabetics with end stage renal disease. Vasa. 2006; 35: 15-20.
19. Faglia E, Clerici G, Clerissi J, Gabrielli L, Losa S, Mantero M, et al. Early and five-year amputation and survival rate of diabetic patients with critical limb ischemia: data of a cohort study of 564 patients. Eur J Vasc Endovasc Surg. 2006; 32: 484-490.
20. Sumpio BE, Lee T, Blume PA. Vascular evaluation and arterial reconstruction of the diabetic foot. Clin Podiatr Med Surg. 2003; 20: 689-708.
21. Mohler E 3rd, Giri J; ACC; AHA. Management of peripheral arterial disease patients: comparing the ACC/AHA and TASC-II guidelines. Curr Med Res Opin. 2008; 24: 2509-2522.
22. Boulton AJ. Pressure and the diabetic foot: clinical science and offloading techniques. Am J Surg. 2004; 187(5A): 17S-24S.
23. Armstrong DG, Lavery LA, Wu S, Boulton AJ. Evaluation of removable and irremovable cast walkers in the healing of diabetic foot wounds: a randomized controlled trial. Diabetes Care. 2005; 28: 551-554.
24. Steed DL. Debridement. Am J Surg. 2004; 187: 71S-74S.
25. Gwynne B, Newton M. An overview of the common methods of wound debridement. Br J Nurs. 2006; 15: S4-S10.
26. Andros G, Armstrong DG, Attinger CE, Boulton AJ, Frykberg RG, Joseph WS, et al. Consensus statement on negative pressure wound therapy (V.A.C. Therapy) for the management of diabetic foot wounds. Ostomy Wound Manage. 2006; Suppl: 1-32
27. Nelson EA, O' Meara S, Golder S, Dalton J, Craig D, Iglesias C. A systematic review of antimicrobial treatments for diabetic foot ulcers. Diabet Med. 2006; 23: 348-359.
28. Lipsky BA. New developments in diagnosing and treating diabetic foot infections. Diabetes Metab Res Rev. 2008; 24 (Suppl 1): S66-S71.
29. Papanas N, Maltezos E. Growth factors in the treatment of diabetic foot ulcers: new technologies, any promises? Int J Low Extrem Wounds. 2007; 6: 37-53.
30. Papanas N, Maltezos E. Advances in treating the ischaemic diabetic foot. Curr Vasc Pharmacol. 2008; 6: 23-28.
31. Petrova N, Edmonds M. Emerging drugs for diabetic foot ulcers. Expert Opin Emerg Drugs. 2006; 11: 709-724.
32. Edmonds ME, Van Acker K, Foster AV. Education and the diabetic foot. Diabet Med. 1996; 13 (Suppl 1): S61-64.
33. Papanas N, Maltezos E, Edmonds M. The diabetic foot: a plea for the elementary? Acta Diabetol. 2006; 43: 152-153.
34. Papanas N, Liakopoulos V, Maltezos E, Stefanidis I. The diabetic foot in end stage renal disease. Ren Fail. 2007; 29: 519-528.
35. Holstein P, Ellitsgaard N, Olsen BB, Ellitsgaard V. Decreasing incidence of major amputations in people with diabetes. Diabetologia. 2000; 43: 844-847.
36. van Houtum WH, Rauwerda JA, Ruwaard D, Schaper NC, Bakker K. Reduction in diabetes-related lower-extremity amputations in The Netherlands: 1991-2000. Diabetes Care. 2004; 27: 1042-1046.
37. El Sakka K, Fassiadis N, Gambhir RP, Halawa M, Zayed H, Doxford M, et al. An integrated care pathway to save the critically ischaemic diabetic foot. Int J Clin Pract. 2006; 60: 667-669.
38. Manes C, Papazoglou N, Sossidou E, Soulis K, Milarakis D, Satsoglou A, et al. Prevalence of diabetic neuropathy and foot ulceration: identification of potential risk factors - a population-based study. Wounds. 2002; 14: 11-15.

39. Doupis J, Grigoropoulou P, Voulgari C, Stylianou A, Georga A, Thomakos P, et al. High rates of co-morbid conditions in patients with type 2 diabetes and foot ulcers. Wounds. 2008: 20: 132-138.
40. Skoutas D, Papanas N, Georgiadis GS, Zervas V, Manes C, Maltezos E, et al. Risk factors for ipsilateral re-amputation in patients with prior amputation for diabetic foot lesions. Int J Lower Extrem Wounds. 2009; 8: 69-74.
41. Papanas N, Tziakas D, Maltezos E, Kekes A, Hatzinikolaou E, Parcharidis G, et al. Peripheral arterial occlusive disease as a predictor of the extent of coronary atherosclerosis in patients with coronary artery disease with and without diabetes mellitus. J Int Med Res. 2004; 32: 422-428.
42. Tentolouris N, Petrikkos G, Vallainou N, Zachos C, Daikos GL, Tsapogas P, et al. Prevalence of methicillin-resistant Staphylococcus aureus in infected and uninfected diabetic foot ulcers. Clin Microbiol Infect. 2006; 12: 186-189.
43. Karagianni D. Amputations in diabetic patients (Population study). Dissertation. Democritus University of Thrace, 2002.
44. Papazafiropoulou A, Tentolouris N, Soldatos RP, Liapis CD, Dounis E, Kostakis AG, et al. Mortality in diabetic and nondiabetic patients after amputations performed from 1996 to 2005 in a tertiary hospital population: a 3-year follow-up study. J Diabetes Complications. 2009; 23: 7-11.
45. Staramos D, Mikroulis D, Drista E, Lazarides M, Dayantas I. Femorodistal by-pass the extent of approval in Greece. Archives of Hellenic Medicine. 1999; 16: 43-47.
46. Papanas N, Papatheodorou K, Christakidis D, Papazoglou D, Giassakis G, Piperidou H, Monastiriotis C, Maltezos E. Evaluation of a new indicator test for sudomotor function (Neuropad) in the diagnosis of peripheral neuropathy in type 2 diabetic patients. Exp Clin Endocrinol Diabetes. 2005; 113: 195-198.
47. Manes C, Mikoudi K, Sossidou E, Pigas G, Karagianni D, Skoutas D, Fotiadis S. Evaluation of a new indicator plaster in identifying diabetic patients at risk of foot ulceration. Diabetologia. 2004; 47 (Suppl 1): A 376.
48. Papanas N, Gries A, Maltezos E, Zick R. The steel ball-bearing test: a new test for evaluating protective sensation in the diabetic foot. Diabetologia. 2006; 49: 739-743.
49. Liatis S, Marinou K, Tentolouris N, Pagoni S, Katsilambros N. Usefulness of a new indicator test for the diagnosis of peripheral and autonomic neuropathy in patients with diabetes mellitus. Diabet Med. 2007; 24: 1375-1380.
50. Tentolouris N, Achtsidis V, Marinou K, Katsilambros N. Evaluation of the self-administered indicator plaster Neuropad for the diagnosis of neuropathy in diabetes. Diabetes Care. 2008; 31: 236-237.
51. Papanas N, Papatheodorou K, Papazoglou D, Monastiriotis C, Christakidis D, Maltezos E. A comparison of the new indicator test for sudomotor function (Neuropad) with the vibration perception threshold and the clinical examination in the diagnosis of peripheral neuropathy in subjects with type 2 diabetes. Exp Clin Endocrinol Diabetes. 2008; 116: 135-138.
52. Papanas N, Edmonds M, Maltezos E. Pseudoclaudication as a manifestation of diabetic neuropathy. Diabet Med. 2005; 22: 1608-1610.
53. Migdalis IN, Triantafilou P, Petridou E, Varvarigos N, Totolos V, Rigopoulos A. Lipid peroxides in type 2 diabetic patients with neuropathy. Res Commun Mol Pathol Pharmacol. 2005; 117-118: 5-12.
54. Stamboulis E, Voumvourakis K, Andrikopoulou A, Koutsis G, Tentolouris N, Kodounis A, et al. Association between asymptomatic median mononeuropathy and diabetic polyneuropathy severity in patients with diabetes mellitus. J Neurol Sci. 2009; 278: 41-43.
55. Didangelos TP, Arsos GA, Karamitsos DT, Athyros VG, Georga SD, Karatzas ND. Effect of quinapril or losartan alone and in combination on left ventricular systolic and diastolic functions in asymptomatic patients with diabetic autonomic neuropathy. J Diabetes Complications. 2006; 20: 1-7.
56. Lazarides MK, Giannoukas AD. The role of hemodynamic measurements in the management of venous and ischemic ulcers. Int J Low Extrem Wounds. 2007; 6: 254-261.