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**FACTORS THAT INFLUENCE THE HEALING
PROCESS IN LOWER LIMB ULCERS OF
DIABETIC PATIENTS.**

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PhD thesis was submitted to Faculty of Medicine, School of Health
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«Η έγκριση της διδακτορικής διατριβής από το τμήμα Ιατρικής της Σχολής Επιστημών Υγείας του Πανεπιστημίου Θεσσαλίας δεν υποδηλώνει αποδοχή των γνώμων του συγγραφέα».

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‘I would like to separately thank Prof. Giannoukas for his guidance during those years, and Mr. P.Chan who was the first one to believe in the importance of diabetic foot and enticed me with the idea of this thesis.’

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Preface

As a medical student, you earn so much information and knowledge about diabetic patients and their complications, but only when you see a neglected diabetic foot ulcer with gangrene in A&E department during your surgical rotation, you realize the difficulty in management of the diabetic foot for both the patient and the physician. Thereafter, you watch the residents from every specialty (General Surgery, Orthopedics, Vascular Surgeons, Dermatologists, Endocrinologists or Internal Medicine etc), how hard they try to refer this diabetic patient to each other. Nobody wants to be involved with the management of such a difficult patient. On the other hand, a multidisciplinary team approach including many specialties would be the ideal management for such a patient with foot ulcer in order to increase the likelihood of ulcer healing and limb salvage.

Mr. Philip Chan (who was my supervisor in Sheffield, and a friend of mine now) and Prof. Giannoukas (who is my supervisor and teacher now) encouraged me to undertake this observational study in our region (Thessaly) including the diabetic patients with foot ulcer, and to assess their management and follow up for 12 months. Dr. A. Bargiota (who is the head of the Endocrinology Department) contributed to the management of those diabetic patients and counseled us constantly. Thus,

we tried to apply the principles of a multidisciplinary team approach in a small scale in our University Hospital, with the contribution also of Orthopedics and General Surgeons when needed.

At the beginning, we conducted a survey under the guidance of the Mediterranean League of Angiology and Vascular Surgery (MLAVS) in order to highlight the current trends in the management of diabetic foot among Vascular Specialists practicing in the Mediterranean region.

During the clinical assessment, management and follow up of diabetic patients, we validated the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) questionnaire in Greek population, assessed factors associated with the healing process or limb salvage, and evaluated the impact of their treatment on their quality of life (QOL).

Diabetic foot ulcer is a worldwide problem with a great impact on health care cost, the quality of life of the patient and its social environment and finally on the mortality and morbidity of those patients. Medical society should take more seriously this huge socio-economical clinical problem and not consider it an issue of one physician alone but a problem that need the attention and management of an organized multidisciplinary team.

SHORT CV

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STUDIES

(a) Medical School, Aristotle University of Thessaloniki (2000-2006), (b) Rural GP in health centre of Elasona and Residency in Vascular Surgery, University Hospital of Larisa, Greece (2007-2008), (c) Residency in Vascular Surgery and Cardiology in Northern General Hospital of Sheffield, UK (2008-2009), (d) Residency in General Surgery, Koutlibanio&Triantafilio General Hospital of Larisa, Greece (2009-2012), (e) Residency in Vascular Surgery, University Hospital of Larisa, Greece (2012-until now)

ACADEMIC POSTGRADUATE ACTIVITY.

1. MSc in Endovascular Techniques and Medicine Thesis: “The role of Internal Iliac Artery Occlusion after Endovascular Abdominal Aortic Aneurysm Repair”. Academic Vascular Surgery Unit, Attikon Hospital, University of Athens Medical School, Greece and Department of Surgical Sciences Bicocca, University of Milano, Italy (February 2012)

FELLOWSHIP AND CLINICAL EXPERIENCE.

(a) Scientific Associate in the Department of General Medicine in Renal Dialysis Clinic Patsidis, Larisa, Greece (07/2006-05/2007), (b) Senior House Officer in Cardiology, General Medicine and Surgery rotation in Koutlibanio&Triantafilio General Hospital of Larisa, Greece (06/2007-09/2007), (c) Senior House Officer in General Medicine in Health Centre of Elassona, Greece (09/2007-12/2007), (d) Senior House Officer in Vascular Surgery, University Hospital of Larisa, Greece (12/2007-09/2008), (e) Senior House Officer in Vascular Surgery, Northern General Hospital of Sheffield, UK (09/2008-12/2008), (f) Senior House Officer in Cardiology, Northern General Hospital of Sheffield (12/2008-03/2009), (g) Senior House Officer in Vascular Surgery, Doncaster

General Hospital, UK (04/2009-06/2009), (h) Resident in General Surgery, Koutlibanio&Triantafilio General Hospital of Larisa, Greece (06/2009-01/2012), (i) Doctor in Special Forces of Greek Army (02/2012-11/2012), (j) Resident in Vascular Surgery, University Hospital of Larisa, Greece (11/2012-until now).

RESEARCH ACTIVITY

Seven (7) Research Protocols in the **Department of Vascular Surgery, University of Thessaly Medical School**, as Resident in Vascular Surgery:

1. **AAA SCREENING**: The value of screening in the detection of Abdominal Aortic Aneurysms in men >60 years in Central Greece.
2. **ACST-2**: A large simple international randomised trial comparing carotid endarterectomy versus carotid artery stenting to prevent stroke.
3. **XALIA**: Xarelto® for Long-term and Initial Anticoagulation in Venous Thromboembolism.
4. **ΤΑΛΩΣ**: Superficial thrombophlebitis: complications, treatment and patients' profile in Greece.
5. **GSK576428**: Superficial venous thrombosis- Fondaparinux

6. **PREVENT**: Prevalence of Deep Venous Thrombosis (DVT) in patients with cancer.
7. **SEVEN**: Superficial venous thrombosis- LEO

Publications in International Journals: 31

Publications in Greek Journals: 2

Oral presentations in International Congresses: 19

Poster in International Congresses: 4

Oral presentations in Greek Congresses: 4

Poster in Greek Congresses: 2

Book chapters: 2

Prizes- Awards - Scholarships: 1

Invited Lectures in International Congresses: 3

Academic Cooperation with other Departments: 1

Organization of Congresses, Courses: 2

Member of scientific societies: 1

Part A

1. Introduction

Diabetes mellitus (DM) is a group of metabolic diseases characterized by chronic hyperglycemia resulting from defects in insulin secretion, insulin action, or both. Metabolic abnormalities in carbohydrates, lipids, and proteins result from the importance of insulin as an anabolic hormone. Low levels of insulin to achieve adequate response and/or insulin resistance of target tissues, mainly skeletal muscles, adipose tissue, and to a lesser extent, liver, at the level of insulin receptors, signal transduction system, and/or effect or enzymes or genes are responsible for these metabolic abnormalities. The severity of symptoms is due to the type and duration of diabetes.¹ One of the most insidious and life threatening complication and even in some cases clinical presentation is diabetic foot ulcer (DFU).

According to the World Health Organization (WHO), it is possible to encompass all foot complications in the term diabetic foot syndrome

that has been defined as “ulceration of the foot associated with neuropathy and different grades of ischemia and infection.”²

The medical and surgical management of DFU should have as its basis a thorough understanding of the complications and metabolic consequences of DM and a multidisciplinary approach from co-operating specialties.

2. History of wound healing

Human’s struggle against wound healing is as old as itself.³ The first report in history was described by Egyptians who repaired their wounds with primitive suture materials and used clean sheets on surgical field to prevent ‘suppuration’. In Greece, Hippocrates had developed treatment methods for primary and chronic wounds. He used various gauze materials empirically such as wine, milk, honey and other substances in open wounds which have lot similarities with our treatment options today. For example wine may suppress pseudomonas proliferation, complex sugar of honey are known to suppress the growth of Gram-positive bacteria and milk products may contains cytokines or serve as buffers to control wound pH. Although the ancients did not know the composition of pus, they had understood that the drainage of localized

products of infection was a good sign. In cases when signs of inflammation could not be localized, they had understood that death would follow. During the early Roman era, even though Celsius was not aware of the existence of bacteria, he recognized and described the cardinal signs of clinical infection being: erythema (rubor), swelling (tumor), pain (dolor) and heat (calor).^{3,4}

The ancients reached by their available means a scientific approach to wound healing by their observations, rationale and conclusions. However, the sequel was not the expected one. During the Dark Ages the domination of the church over the thought process overran the free thinkers in the arts and the sciences. Nevertheless, great minds interested in science, anatomy and evolution could not be suppressed. In the 17th century, John Hunter was the first one to describe angiogenesis. In the 18th and 19th centuries came the recognition that a factor passed from care givers to patients, would kill them. These observations were made by Holmes, Sommelweiss and many others which promoted the discovery of bacteria by Pasteur and the concept of antisepsis by Lister.^{3,5}

It was Claude Bernard (1813-1878) who really played a major role in development of laboratory methods for the of clinical medicine and thus advancements that would evolve wound healing treatment in general and diabetic wounds in particular. The late 19th to mid-20th century saw

the evolution of antibiotics which had more positive effects on wound healing than negative ones. Thus Fleming and his associates (Chain and Florey) discovered penicillin by studying the mold. Keen and simple observations had changed the course of medical history for the better.³

However, in the 1940s was the first time in history that healing studies involved cell cultures, animal models and eventually human studies. Alexis Carrel was the father of modern day wound healing studies. He grew fibroblasts in cultures, studied wound contraction in World War I combat injuries and did the first microsurgery for which he was awarded the Nobel Prize. By the end of World War II, Egbert Dumphy, at Harvard, started a series of experiments in animals and humans examining a number of factors including nutrition, oxygen, shock and so on. Stan Levinson experienced on burn victims, shock and their metabolism. These two surgical leaders published the first texts and symposium on wound healing and inspired and trained future leaders in wound healing research.³

Since the 1970s there had been a logarithmic growth in the laboratory tools available to seek answers to the mystery of wound healing pathogenesis in general and diabetic wounds in particular, such as tissue cultures, electron microscopy, protein analysis, Western blot, Northern blot, PCR (polymerase chain reaction) and now gene array.

Perhaps, the last one; the defining structure and means for analysis of DNA and RNA was the greatest discovery of all. Rosalind Fraklin, Watson and Crick led the advancements to identify rapidly protein structure, map genes and characterize materials with great speed accuracy. The aggregation of biological information for wound healing process and its treatment was dramatically increased those last years. Those discoveries have created new prospects for our understanding and treatment of the diabetic wound problem. Many of these advances have been resulting from Federal Governments and via National Institutes of Health. However, unfortunately in recent and present history the most interesting phenomenon is the discovery that wound care is a market worth billions of money, which is something that could be extremely dangerous for the diabetic foot patients and their treatment in the near future.³

3. Epidemiology

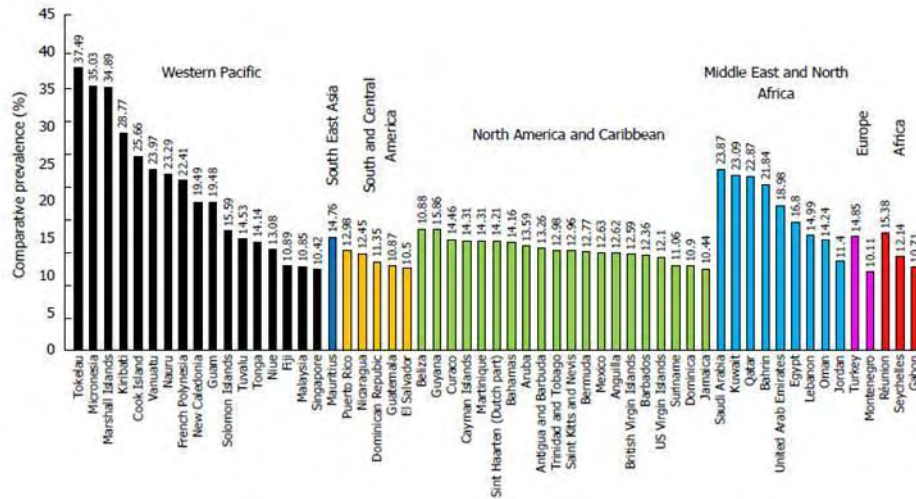
The classical classification of diabetes as proposed by the American Diabetes Association (ADA) in 1997 as type 1, type 2, other types, and gestational diabetes mellitus (GDM) is still the most accepted classification and adopted by ADA.¹ During past decades, a distressing

increase in the prevalence of diabetes has been observed and especially in DM II. In the Framingham study, the prevalence had risen from 0.9% in 1958 to 3% in 1995.⁶ Later on, the centers for disease control in 2001 estimated the US prevalence of diagnosed DM at 7.3% which was quite higher in comparison with a similar study in 1990 reporting 4.9%, representing nearly a 48% increase over the decade.⁷ Recently, in the year 2009, the estimated number of youth in the United States younger than 20 years with type 1 diabetes was recorded 166984.⁸ The prevalence of type 1 diabetes in the world is not known but in the United States in youth younger than 20 years was 1.93 per 1000 in 2009 (0.35-2.55 in different ethnic groups) with 2.6%-2.7% relative annual increase.⁹ In addition, nowadays there are many individuals with prediabetes who do not meet the criteria of having diabetes but are at high risk to develop type 2 diabetes in the future. According to the ADA Expert Committee, prediabetes is defined as pathological condition in cases in which either impaired fasting plasma glucose (IFG) levels are between 100-125 mg/dL (5.6-6.9 mmol/L) or impaired glucose tolerance test (IGT) with 2-h plasma glucose levels in the oral glucose tolerance test (OGTT) is between 140-199 mg/dL (7.8-11.0 mmol/L). However the WHO still adopts the range for IFG from 110-125 mg/dL (6.1-6.9 mmol/L).¹⁰ In 2013, it was reported by the International Diabetes Federation (IDF) that

the global prevalence of diabetes in adults is 8.3% (382 million people), with 14 million more men than women (198 million men vs 184 million women).¹¹

The higher prevalence was noticed between the ages 40 and 59 years and the number is expected to rise beyond 592 million by 2035 with a 10.1% global prevalence.¹¹ The Middle East and North Africa region has the highest prevalence of diabetes (10.9%), however, Western Pacific region has the highest number of adults diagnosed with diabetes (138.2 millions) and has also countries with the highest prevalence.⁹ Most of the cases are being presented in low- and middle income countries in 80% of the cases, “where the epidemic is gathering pace at alarming rates”. (Figure 1) It is of note, that indigenous people of America and Polynesia are those with the highest risk; the Pima tribe in Arizona has the highest prevalence of DM II in the world, affecting nearly 50% of all adult members.

Figure 1. Comparative prevalence of diabetes in adults (20-79 years) in countries with high prevalence (>10%).



In accordance to this rise of DM prevalence worldwide, is the increase of DFU incidence among diabetic patients. This is a reality that is taking place not only in developing countries, but in developed ones too although they have evolved their health systems. For example in Denmark, approximately 22,000 diabetic Danish patients are diagnosed with DFU, and each year approximately 3,000 new patients are added to this population.¹² In Canada, Out of 2.7 million patients living with DM in 2010, the probability of developing DFU in their lifetime was 15 percent/year.¹³ In the US, DFU prevalence among persons aged 44 years was 6.5/1000 diabetics and it rose progressively to 10.3/1000 diabetics in individuals aged 75 years. In addition, the rate of hospital discharges with

DFU for 1000 diabetic patients rose from 5.4 in 1980 to 6.9 in 2003.¹⁴

These results are becoming worse in developing countries, such in Africa countries in which the frequency of diabetic patients with DFU may reach in some areas as high as 69%.¹⁵

It is apparent that DFU was always a multinational burden and this concept yielded results starting with the St. Vincent Declaration which was a set of goals for the health care of people with DM and was published as the product of an international conference held in St. Vincent, Italy, on 10-12 October 1989.¹⁶ Representatives of government health departments and patients' organizations from most European countries met with diabetes experts under the aegis of the WHO Europe and the IDF Europe. General standards for diabetes care were agreed on, as well as plans for improving care and in particular diabetic foot care in participating countries toward the goals. Consequently the St Vincent Declaration inspired other regional partnerships between the IDF and WHO, especially in response to the emerging pandemic of DM II: the Declaration of the Americas or DOTA (1996), the Western Pacific Declaration on Diabetes (WPDD 2000), and the Declaration and Diabetes Strategy for Sub-Saharan Africa (2006).

4. Health care cost

The cost of care for diabetic patients with DFU is a major economic burden worldwide in comparison with the management of diabetic patients without ulceration. Cost will play an ever-increasing role because third-party payers cannot reimburse all therapies used to treat DFU in every country and for every patient.

During past decades many studies have taken place, trying to estimate and unmask the magnitude of cost related to DFU worldwide. An analysis of Medicare claims data from 1995 to 1996 showed that expenditures for DFU patients were three times higher than for the general population (\$15,309 vs \$5226), yielding a total cost for Medicare in 1995 of \$1.5 billion.¹⁷ Lower extremity ulcers accounted for 24% of the overall cost for diabetic population with an ulcer. Most of the ulcer-related costs accrued on the inpatient side (73.7%); proportionately smaller amounts went to physicians and nursing home facilities.¹⁷ Ramsey et al.¹⁸ demonstrated in a retrospective nested case-control study that the relative cost of care for diabetic patients with DFU ranges from 1.5 to 2.4 times higher than that of diabetic patients without an ulcer in the year before diagnosis to 5.4 times higher in the year after the ulcer episode. The cost of care for diabetic patients with DFU showed a

tendency to return to the non-ulcer group only after 2 years from the first diagnosis, but was still 2.8 times higher. Excess cost was \$26,490 in ulcer patients during the year of the ulcer episode and \$4927 for diabetic patients without an ulcer. The excess cost persisted during the second year after the ulcer episode. Diabetic patients with DFU had more inpatient hospital days than diabetic patients without ulcers (6.03 vs 1.46 days), and this difference was still significant 1 year after the ulcer episode (4.06 vs 2.61). In addition, diabetic foot patients had more emergency department visits during the first year of the study (0.42 vs 0.18) and more non-emergency outpatient visits (35.08 vs 13.05).¹⁸

In a retrospective economic analysis based on a prospective study of consecutively presenting diabetic patients admitted to the Department of Internal Medicine because of foot ulcer, Apelqvist et al.¹⁹ monitored 314 patients. Almost half of the patients (54%) healed in 2 months, 19% healed in 3 to 4 months, and 27% healed in 5 months. Healing without amputation averaged \$6664, whereas healing by amputation averaged \$44,790. Hospitalization costs and topical treatment of ulcers accounted for most of the costs. For patients that healed without amputation, 37% and 45% of the total costs were for hospitalizations and ulcer treatments, and for patients that healed with amputations, 65% of total costs were for hospitalizations and 13% for ulcer treatments.¹⁹ Those patients were

treated and followed prospectively long term. A retrospective economic analysis was performed of costs for 274 patients during 3 years who continued to be part of the study from healing of an initial foot ulcer, with or without amputation. Expected total present value cost per patient during 3 years of observation was \$26,700 (U.S. dollars) for primary healed patients with critical ischemia and \$16,100 for primary healed patients without critical ischemia. For patients who healed with an amputation, the corresponding costs were \$43,100 after a minor amputation and \$63,100 after a major amputation.²⁰

Another retrospective study of diabetic patients with DFU demonstrated an average cost per ulcer episode of \$13,179. In this study there was an increase in cost according to ulcer depth and severity as evaluated by the Wagner classification system.²¹ Costs associated with a simple ulcer averaged \$1892, and more severe ulcers averaged \$27,721. This study confirmed the high impact of inpatient stay as being 77% of the overall cost. Progression from simple ulcer cases to more complex ones carried an additional increase in cost of \$20,136.²¹

Studies that have been published recently demonstrated that the economical burden of DFU treatment remains important. Skrepnek et al.²² conducted a cross-sectional study utilized Agency for Healthcare Research and Quality (AHRQ) Healthcare Cost and Utilization Project

(HCUP) National Emergency Department Sample (NEDS) discharge records of emergency department cases among persons >18 years with any-listed diagnosis of DFU. They recorded 1,019,861 cases of diabetic foot complications presented to emergency department in the US from 2006–2010, comprising 1.9% of the 54.2 million total diabetes cases. The mean patient age was 62.5 years and 59.4% were men.²² The national cost was \$1.9 billion per year in the emergency department for diabetic patients and \$8.78 billion per year (US\$) including inpatient charges among the 81.2% of cases that were admitted.²²

Recently Caitlin et al.²³ analyzed the Nationwide Inpatient Sample (2005-2010) using the International Classification of Diseases, Ninth Revision codes for a primary diagnosis of diabetic foot ulceration. It was demonstrated that for the 336,641 patients who were admitted with a primary diagnosis of diabetic foot ulceration (mean age, 62.9 years, 59% male, 61% white race) the annual cumulative cost for inpatient treatment of DFS increased significantly from 2005 to 2010 (\$578,364,261 vs \$790,017,704; $p < 0.001$). In addition, more patients were hospitalized (128.6 vs 152.8 per 100,000 hospitalizations; $p < 0.001$), and the mean adjusted cost per patient hospitalization increased significantly over time (\$11,483 vs \$13,258; $p < 0.001$). Based on multivariable analysis, the

main factors contributing to the escalating cost per patient hospitalization included increased patient co morbidities, open revascularization (unadjusted \$15,145 [RI, 1.25] vs adjusted \$30,759 [RI, 1.37]), endovascular revascularization (unadjusted \$17,662 [RI, 1.29] vs adjusted \$28.937 [RI, 1.38]), and minor amputations (unadjusted \$9918 [RI, 1.24] vs adjusted \$18,084 [RI, 1.33]) (P < .001, all).²³

Even in countries with well organized health system like Canada the economical burden remains important negative factor. In Canada in the year 2011, DFS was associated with 16,883 hospital admissions (327,140 days). This acute institution care represented \$320.5 million, and with an additional \$125.4 million for home care and \$63.1 million for long term care, the annual cost associated with DFS-related care was \$547.0 million, or \$21.371 annual cost per prevalent case. For an incident case of DFS, the average 3-year cumulative cost was \$52.360.¹³ Another example, is Denmark, in which the median cost for the treatment of a DFS patient was estimated 17.900 Euros.¹²

5. Clinical examination and diagnosis

5.1 Etiology

The etiology of DFS in diabetic patients is commonly associated with peripheral neuropathy and peripheral arterial disease or both entities, therefore each ulcer can be classified as neuropathic (figure 2), ischemic (figure 3) or neuroischemic (figure 4). Neuroischaemia is the combined effect of diabetic neuropathy and ischaemia, whereby macrovascular disease and, in some instances, microvascular dysfunction impair perfusion in a diabetic foot.²⁴



Figure 2. Neuropathic ulcer.



Figure 3. Ischemic ulcer.



Figure 4. Neuroischemic ulcer.

- **Peripheral neuropathy**

Peripheral neuropathy is the major component of nearly all diabetic ulcerations, and may predispose to DFU through its effects on the sensory, motor and autonomic nerves.²⁵ The loss of protective sensation experienced by patients with sensory neuropathy renders them vulnerable to physical, chemical and thermal trauma. This is defined as a level of sensory loss that allows patients to injury themselves without recognizing neither the injury itself as an event nor infection. In addition, motor neuropathy can cause foot deformities (such as hammer toes and claw foot), which may result in abnormal pressures over bony prominences. This is taking place, when diabetic neuropathy causes atrophy of intrinsic musculature of the hand and foot. When this occurs, the extrinsic musculature works unopposed causing hammering of the toes and retrograde buckling of the metatarsal heads. Thus, both the toes (dorsally) and the metatarsal heads (plantary) are more prominent and therefore more prone to ulceration. Finally autonomic neuropathy is typically associated with dry skin, which can result in fissures, cracking and callus which could lead easier to ulcer formation while additionally bounding pulses can be often misinterpreted as indicating a good circulation.²⁶

Generally every physician should remember that the presence of neuropathy in diabetic patients is associated with a seven-fold increase in risk of ulceration.²⁷

- **Peripheral arterial disease.**

On the other hand, diabetic patients are twice as likely to have peripheral arterial disease (PAD) as those without diabetes.²⁸ The proportion of patients with an ischemic component to their DFU is increasing and it is reported to be a contributory factor in the development of DFU in up to 50% of diabetic patients.^{26,29} It is important to remember that even in the absence of a poor arterial supply, microangiopathy (small vessel dysfunction) also may contribute to poor ulcer healing in neuroischaemic DFU.³⁰ Decreased arterial perfusion in the diabetic foot is a complex scenario and is characterised by various factors relating to microvascular dysfunction in addition to macrovascular dysfunction.³⁰ It is also noteworthy that diabetic patients with the sequelae of atherosclerotic disease often present at an earlier stage than their counterparts without diabetes. Additionally, diabetic patients often have a unique distribution of atherosclerosis at the arterial level. Unlike with non-diabetic patients, occlusive disease in diabetic patients has a

distinct propensity to occur in the infragenicular vessels in the calf. The affected arteries, namely the anterior and posterior tibial and less the peroneal artery are more severely affected and are more likely to present with occlusion in diabetic patients. Although these arteries are preferentially affected, the proximal arteries to the level of the popliteal artery are often spared in diabetic patients. Equally important is the observation that the dorsalis pedis artery is commonly spared from the occlusive disease in diabetic patients.^{26,29,30}

Table 1. Typical features of DFU according to the etiology.³¹

Feature	Neuropathic	Ischaemic	Neuroischaemic
Sensation	Sensory loss	Painful	Degree of sensory loss
Callus/necrosis	Callus present and often thick	Necrosis common	Minimal callus Prone to necrosis
Wound bed	Pink and granulating, surrounded by callus	Pale and sloughy with poor granulation	Poor granulation
Foot temperature and pulses	Warm with bounding pulses	Cool with absent pulses	Cool with absent pulses
Other	Dry skin and fissuring	Delayed healing	High risk of infection
Typical location	Weight-bearing areas of the foot, such as metatarsal heads, the heel and over the dorsum of clawed toes	Tips of toes, nail edges and between the toes and lateral borders of the foot	Margins of the foot and toes

5.2 Assessing the diabetic foot

Patients with a DFU need to be assessed holistically and intrinsic and extrinsic factors considered. Patients with DFU should be assessed by a multidisciplinary diabetic foot team (MDFT) of physicians within one working day of presentation or even immediately in the presence of severe infection.^{32,33} However, in reality in most hospitals, a MDFT approach does not exist and physicians have to work as individuals on DFU diagnosis and management.

Primary health-care physicians should always record the full patient history including medication, co morbidities and risk factors for DFU and current DM status. They should also take into consideration in particular the history of the wound, previous DFU or amputation and any symptoms suggestive of neuropathy or PAD.²⁶

5.2.1 Ulcer documentation

The first clinical step for the physician is to record and document the ulcer's characteristics. Thus the physician has to answer himself simple but important questions:³⁴

- Is the wound predominantly neuropathic, ischemic or neuroischemic?
- If ischemic, is there critical limb ischemia?
- Are there any musculoskeletal deformities?
- What is the size/depth/location of the wound?
- What is the color/status of the wound bed?
 - Black (necrosis)
 - Yellow, red, pink
- Is there any exposed bone?
- Is there any necrosis or gangrene?
- Is the wound infected? If so, are there systemic signs and symptoms of infection (such as fevers, chills, rigors, metabolic instability and confusion)?
- Is there any malodour?
- Is there local pain?
- Is there any exudation? What is the level of production (high, moderate, low, none), color and consistency of exudation, and is it purulent?
- What is the status of the wound edge (callus, maceration, erythema, edema, undermining)?

It is helpful for the physician at the first consultation to digitally photograph the diabetic ulcer and periodically thereafter to document progress.³⁵ This is particularly useful for ensuring consistency of care among healthcare practitioners during various examinations, facilitating the health in remote areas and illustrating improvement to the patient.³⁵

5.2.2 Diabetic Neuropathy

As it was described previously, diabetic neuropathy is the major component of diabetic ulcer.^{25,26,27} Thus, the consequent vulnerability to physical and thermal trauma increase the risk of ulcer formation. There are two simple and one a little more complicated tests which are effective in diagnosis of peripheral neuropathy and are commonly used. The first two tests are the 10g Semmes-Weinstein Monofilament (SWM) and the tuning fork, and the third one is vibration perception threshold (VPT) meter.

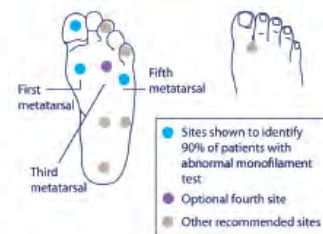
The 10g SWM is the most frequently used screening tool to determine the presence of neuropathy in patients with diabetes. It should be applied at various sites along the plantar aspect of the foot. Guidelines vary in the number of sites advocated, but the international consensus is to test at three sites (Figure 5).³⁶ A positive result is the inability to feel

the monofilament when it is pressed against the foot with enough force to bend it. In prospective studies, the SWM identified persons at high risk of foot ulceration with a sensitivity of 66-91%, a specificity of 34-86%, a positive predictive value of 18-39% and a negative predictive value of 94-95%.^{37,38}

Figure 5. Procedure for carrying out the monofilament test adapted from International Working Group on the Diabetic Foot organization.³⁶

The International Working Group on the Diabetic Foot (IWGDF) recommends the following procedure for carrying out the monofilament test.

- The sensory examination should be carried out in a quiet and relaxed setting
- The patient should close their eyes so as not to see whether or where the examiner applies the monofilament
- The patient should sit supine with both feet level
- First apply the monofilament on the patient's hands or on the inside of the arm so they know what to expect
- Apply the monofilament perpendicular to the skin surface with sufficient force to bend or buckle the monofilament
- Ask the patient:
 - Whether they feel the pressure applied (yes/no)
 - Where they feel the pressure (left foot/right foot)
- Apply the monofilament along the perimeter of (not on) the ulcer site
- Do not allow the monofilament to slide across the skin or make repetitive contact at the test site
- The total duration of the approach (skin contact and removal of the monofilament) should be around 2 seconds
- Apply the monofilament to each site three times, including at least one additional 'mock' application in which no filament is applied
- Encourage the patient during testing by giving positive feedback
 - Protective sensation is present at each site if the patient correctly answers two out of three applications
 - Protective sensation is absent with two out of three incorrect answers



Using a monofilament to test for neuropathy

Note: The monofilament should not be used on more than 10 patients without a recovery period of 24 hours

Be aware that patients with small nerve fibre damage and intact sensory nerves may have a painful neuropathy. They may describe sharp, stabbing, burning, shooting or electric shock type pain, which may be worse at night and can disrupt sleep. The absence of cold warm discrimination may help to identify patients with small nerve fibre damage.³⁹ In addition, the physicians should not test for neuropathy the patients in areas of callus as this can mask feeling from any of the neuropathy testing devices and may give a false-positive result.

The conventional tuning fork is also an easy and inexpensive tool to assess vibratory sensation. The test is considered positive when the patient loses vibratory sensation whereas the examiner still perceives it.²⁷ It has been demonstrated that graduated tuning fork (Rydel-Seiffer) fork (figure 6) have yielded comparable results to biothesiometer ($r=-0.90$; $p<0.001$).⁴⁰

Figure 6. A modern Rydel-Seiffer fork.⁴¹



Finally the VPT meter is another useful valuable instrument to assist in clinical evaluation of diabetic neuropathy. It is semi quantitative and is potentially less prone to interoperator variation than SWM device. The VPT meter also known as Biothesiometer or Neurothesiometer, is a handheld unit which is connected by an electrical cord to a base unit (figure 7). A mean of three readings measured in Volts (V), is generally used to determine the VPT for each foot. In a prospective study, a VPT of more than 25 V had a sensitivity of 83%, a specificity of 63%, a positive likelihood ratio of 2.2 and a negative likelihood ratio of 0.27 for predicting foot ulceration.⁴²

Figure 7. A modern Biothesiometer or Neurothesiometer.⁴²



In 2001, Bennet M,⁴³ at the Chronic Pain Management Service (CPMS) at St. James's University Hospital, Leeds developed LANSS Pain Scale: the Leeds assessment of neuropathic symptoms and signs. This study described the development and validation of a novel tool for identifying patients in whom neuropathic mechanisms dominate their pain experience which was based on SWM but with the use of 23 gauge needle.

This previous study triggered our Vascular Surgery Department's initiative to conduct a study in our center. The aim of the study was to apply the Greek version of the LANSS questionnaire on patients with diagnosed neuropathic pain, to assess its validity and investigate any association of LANNS with visual analog pain scales (VAS-ADL and VAS-INT). Further explanation of the study and visual analog pain scales is being undertaken detailed in the results area.

5.2.3 Vascular evaluation

Medical history of the diabetic patient could be helpful for the initial assessment of the PAD presence.⁴⁴ Intermittent claudication is the earliest and the most common symptom in PAD and may be present as pain, cramping or aching in the calves, thighs or buttocks that appears

reproducibly with walking and is relieved by rest.⁴⁴ During clinical assessment the physician should always palpate peripheral pulses as a routine of the physical examination and include the femoral, popliteal and pedal (dorsalis pedis and posterior tibial) pulses. Assessment of pulses is a learned skill and has a high degree of inter-observer variability, with high false positive and false-negative rates. The dorsalis pedis pulse is reported to be absent in 8.1% of healthy individuals, and the posterior tibial pulse is absent in 2.0%. Nevertheless, the absence of both pedal pulses, when assessed by an experienced clinician, strongly suggests the presence of pedal vascular disease.⁴⁵

The next step in assessing the diagnosis of PAD, is the use of Doppler ultrasound measuring the anklebrachial pressure index (ABPI) and the Doppler waveform which can be used as adjuncts to the clinical findings when carried out by a competent practitioner. Introduced in the late 1960s, the measurement of the ABPI is a simple test used to document PAD in clinical and scientific settings.⁴⁶ It is the ratio of systolic pressures in the lower and upper extremities. Its current pathological value is issued from older studies. Ever since, a reduction in ABI is used as a strong indicator of PAD, thus ABPI values < 0.9 are conventionally used as a pathological threshold to define PAD.⁴⁷

This decrease in ABPI sensitivity can also be explained by arterial stiffness secondary to medial artery calcification (MAC). However, this may result in poorly compressible vessels and a high ABPI. Indeed, high index values (>1.3-1.4) are particularly frequent in diabetic patients,⁴⁸ more specifically when diabetes is concomitant to kidney disease, neuropathy or foot lesions.⁴⁹ In this case, high ABI values and MAC correlate with the duration and severity of diabetes. Therefore, the sensitivity of ABPI seems to be limited in case of complicated or longstanding diabetes leading to more MAC. Moreover, high ABPI could underestimate the prevalence of PAD in diabetes because ABI values between 0.9 and 1.3 would be falsely considered as normal and higher values could not be interpreted. In those cases the toe-brachial index (TBI) may be useful for the diagnosis of PAD in diabetic patient.

The American College of Cardiology Foundation (ACCF) and American Heart Association (AHA) stated in the ACCF/AHA 2011 guidelines that the TBI should be used to establish the lower extremity PAD diagnosis in patients in whom the condition is suspected, and when the ABI test is not reliable due to non-compressible vessels (longstanding diabetes or advanced age).⁵⁰ The evidence supporting this was graded as level B evidence. The ACCF/AHA guidelines had defined a TBI <0.7 as diagnosis for PAD.

Another non-invasive mean of measurement of limb perfusion is transcutaneous oxygen tension (normal >40 mmHg). Patients with occlusive disease have significantly reduced transcutaneous oxygen tension and this has been used to determine the possibility of ulcer healing and optimal amputation healing.⁵¹

In many cases, duplex ultrasound of the leg arteries is useful to diagnose the anatomic location and degree of stenosis of PAD in diabetic patients.⁵² In many centers, in which a Multi-sliced ct angiography (MSCT) angiography is available, although MSCT has not been established as a routine screening method for detection of PAD in diabetics, it could be used for the detection of anatomical lesions in leg ischaemia patients when revascularization is indicated and in those with conflicted reports of vascular duplex ultrasound. It is considered as a substitute for Magnetic resonance angiography (MRA) for patients who have a contraindication for this exam.⁵² MRA is useful in the diagnosis of anatomic lesions and the grade of peripheral artery stenosis after a functional study with indexes is conducted. Selection of the suitability of a lesion for percutaneous revascularization is a second indication for its usage. Both indications are applied in peripheral arterial disease subjects including diabetic subgroups with IA levels of evidence according to AHA/ACC Guidelines.⁵⁰

Digital subtraction angiography (DSA) is indicated in diabetic patients with non-healing ulcers or osteomyelitis requiring endovascular and surgical intervention. Most of these patients, will have severe stenotic-occlusive disease involving all three run-off vessels of the calf (figure 8). In this patient population, 20% of peripheral bypass grafts will have to extend to a pedal artery. The distal anastomosis is either to the dorsalis pedis artery or the proximal common plantar artery trunk.⁵³ Thus, detailed mapping of the arterial disease from abdominal aorta to the pedal vessels is necessary.



Figure 8. DSA of below knee arteries with diffused lesions.

5.2.4 Identifying infection in a diabetic ulcer

Recognizing infection in patients with DFU may be challenging, but it has a major role in the patient's clinical assessment. It is at this

crucial early stage that physicians has the potential to curb what is often progression from simple (mild) infection to a more severe problem, with necrosis, gangrene and often amputation.⁵⁴ Around half of diabetic ulcers (56%) become infected and overall about 20% of patients with an infected foot ulcer will undergo a lower extremity amputation.⁵⁵ Thus, a diagnosis of diabetic foot infection should be made using clinical signs and symptoms and not just microbiological results. All open wounds will be colonized with organisms, making the positive culture difficult to interpret. The International Working Group on the Diabetic Foot (IWGDF) and the Infectious Disease Society of America (IDSA) have developed validated clinical criteria for recognising and classifying diabetic foot infection as it is shown in table 2.⁵⁶ According to this classification there are 4 grades of diabetic foot infection severity; grade 1 the uninfected, grade 2 mild one, grade 3 moderate one and grade 4 the severe one.

Clinical criteria	Grade/severity
No clinical signs of infection	Grade 1/uninfected
Superficial tissue lesion with at least two of the following signs: — Local warmth — Erythema >0.5-2cm around the ulcer — Local tenderness/pain — Local swelling/induration — Purulent discharge Other causes of inflammation of the skin must be excluded	Grade 2/mild
Erythema >2cm and one of the findings above or: — Infection involving structures beneath the skin/ subcutaneous tissues (eg deep abscess, lymphangitis, osteomyelitis, septic arthritis or fascitis) — No systemic inflammatory response (see Grade 4)	Grade 3/moderate
Presence of systemic signs with at least two of the following: — Temperature >39°C or <36°C — Pulse >90bpm — Respiratory rate >20/min — PaCO ₂ <32mmHg — White cell count 12,000mm ³ or <4,000mm ³ — 10% immature leukocytes	Grade 4/severe

Table 2. Classification and severity of diabetic foot infection.

Additionally, accurate diagnosis in the patient with diabetes translates to differentiation between bone and soft tissue infection. Thus, imaging modalities are useful in this evaluation. A plain radiography (X-ray) remains the first screening examination on every diabetic patient with suspected infection. Both soft tissue edema and cellulitis display increased density and thickening of the subcutaneous fat. Infection may result in blurring of the usually visible fat planes. Ulcers may or may not be visible depending on their size and the orientation. However, the

presence of soft tissue swelling, periosteal new bone fracture, cortical bone destruction, focal osteopenia and permeative radiolucency are diagnostic for osteomyelitis. These osseous changes only become evident after osteomyelitis has been present for 10-14 days and require up to 50% bone loss before becoming apparent on x-ray.⁵⁷ The sensitivity of the X-ray ranges 52-93% and specificity 33-92% for the detection of osteomyelitis. On the other hand Computed Tomography (CT) scan is superior to X-ray in detection of cortical destruction, periostitis and soft tissue or intraosseous gas. Particularly during early stages, these findings of acute osteomyelitis may be difficult to detect on plain X-ray, but they can be assessed on CT.⁵⁸ However, Magnetic resonance imaging (MRI) is presently considered the investigation of choice for diagnosing diabetic foot osteomyelitis.⁵⁹ In osteomyelitis, the loss of signal in T₁-weighted images and higher intensity on T₂-weighted images can reveal the pathology as early as 3 days after infection. A meta-analysis has demonstrated MRI is probably the most useful imaging modality for assessing osteomyelitis with a sensitivity of about 90% and a specificity of about 80%.⁶⁰

There are more diagnostic modalities for diabetic foot infection, but they are not available in every centre, they are more expensive and they are not used broadly and neither in our University Hospital. Thus

there will be no detailed description. These are: Bone scintigraphy (three-phase bone scan using Technetium-99m-Medronic Acid Bisphosphonate provides a two-dimensional image of areas in bone with active bone turnover), single photon emission computerized tomography (SPECT) (combines bone scan with CT to improve the anatomical–functional correlation since it provides three-dimensional images of the foot), White blood cell scan (Leukocytes can also be removed from the patient, tagged with a radioactive tracer and re-infused into the patient where they accumulate at an infected focus), and Positron emission tomography (PET scan).⁶¹

One equally important step to imaging during diagnosis of diabetic foot ulcer infection, is the physicians to take appropriate cultures, preferably soft tissue (or bone when osteomyelitis is suspected), or aspirations of purulent secretions.⁵⁶ Some advocate using a deep swabbing technique after the wound has been cleansed and debrided.⁶² In some cases superficial swabbing has been shown to be inaccurate as swab cultures are likely to grow surface contaminants and often miss the true pathogen(s) causing the infection.⁵⁶ In those cases tissue specimens or deep swabs should therefore be cultured for both aerobic and anaerobic organisms.

5.2.5 Identifying foot deformities

As it was mentioned in 5.1, motor neuropathy can cause foot deformities (such as hammer toes and claw foot), which may result in abnormal pressures over bony prominences. Thus, both the toes (dorsally) and the metatarsal heads (plantary) are more prominent and therefore more prone to ulceration (figure 9).^{25,26,27,56}

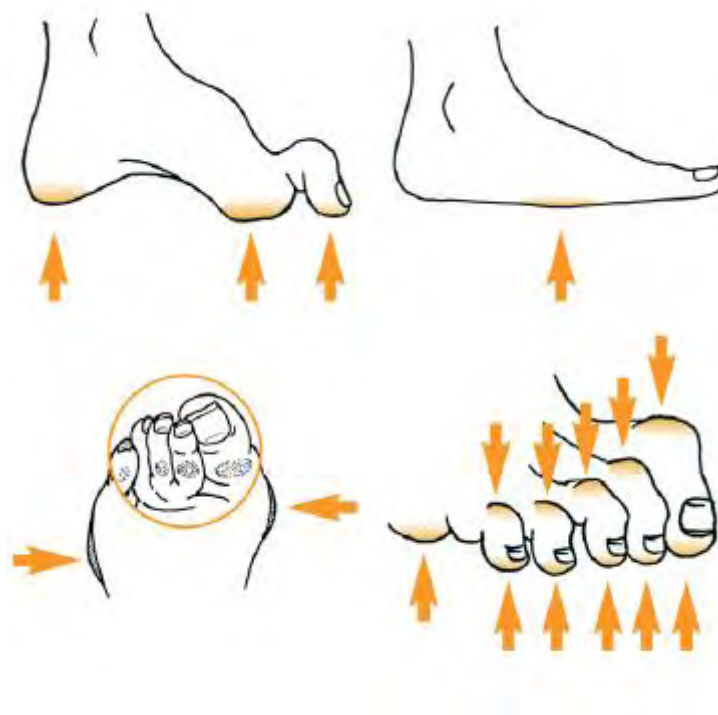


Figure 9. Prominent areas to ulceration due to diabetic foot deformities.

Additionally, these patients may also develop atypical walking patterns (Figure 10). The altered biomechanical loading of the foot can result in callus, which increases the abnormal pressure and can cause subcutaneous haemorrhage.³⁶ One clinical condition with diabetic foot deformity is Charcot joint and should be immediately diagnosed. Charcot joint is a form of neuroarthropathy that occurs most often in the foot and in people with diabetes.⁶³ Nerve damage from diabetes causes decreased sensation, muscle atrophy and subsequent joint instability, which is made worse by walking on an insensitive joint. In the acute stage there is inflammation and bone reabsorption, which weakens the bone. In later stages, the arch falls and the foot may develop a 'rocker bottom' appearance (figure 10).



Figure 10. Patients had developed atypical walking patterns, resulting in infected ulcer and gangrene.

5.2.6 Classification of diabetic foot ulcer

Diabetic foot ulcer is without doubt an important social-economical burden worldwide. Therefore, various wound classification systems have been developed, so there will be a common ‘language’ among the physicians who are involved in the diabetic foot management. Classification systems grade ulcers according to the presence and extent of various physical characteristics, such as size, depth, appearance and location. These systems can help in the planning and monitoring of treatment and in predicting outcome.^{62,64} and also for research and audit.

Classification systems should be used consistently across the healthcare team and be recorded appropriately in the patient's records.

One well-established system widely used is the new University of Texas (UT) diabetic wound classification system (figure 11).⁶⁵ According to this classification there are 4 stages depending on the presence of infection or/and ischemia combined with 4 grades of wound state.

University of Texas Diabetic Wound Classification System				
Stage	Grade			
	0	I	II	III
A (no infection or ischemia)	Pre- or post-ulcerative lesion completely epithelialized	Superficial wound not involving tendon, capsule, or bone	Wound penetrating to tendon or capsule	Wound penetrating to bone or joint
B	Infection	Infection	Infection	Infection
C	Ischemia	Ischemia	Ischemia	Ischemia
D	Infection and ischemia	Infection and ischemia	Infection and ischemia	Infection and ischemia

Figure 11. University of Texas (UT) diabetic wound classification system.⁶⁵

A more comprehensive scoring system for an infected diabetic ulcer could help clinicians determine the need for hospitalization, the urgency of undertaking diagnostic tests or surgical interventions, and the type and route of antimicrobial therapy. Thus, Lipsky et al.⁶⁶ developed a

diabetic foot infection (DFI) wound score system (Table 3) that incorporates grading of both a wound's measurements and specific parameters related to local and systemic signs and symptoms of infection. They have used data obtained from patients enrolled in SIDESTEP (Study of Infections in Diabetic feet comparing Efficacy, Safety and Tolerability of Ertapenem versus Piperacillin/tazobactam) with a diabetic foot infection, which was a randomized, multicenter, antibiotic treatment trial.⁶⁷

i.

Item	Assessment	Preassigned scoring
Wound parameters		
Purulent discharge	Absent	0
	Present	3
Other signs and symptoms of inflammation	Absent	0
Nonpurulent discharge	Mild	1
Erythema	Moderate	2
Induration	Severe	3
Tenderness		
Pain		
Local warmth		
Range of wound parameter (10-item) subtotal		0-21
Range of wound parameter (eight-item) subtotal		0-15
Wound measurements		
Size (cm ²)	<1	0
	1–2	1
	> 2–5	3
	> 5–10	6
	> 10–30	8
Depth (mm)	> 30	10
	<5	0
	5–9	3
	10–20	7
Undermining (mm)	> 20	10
	<2	3
	2–5	5
	>5	8
Range of wound measurement subtotal		3–28
Range of total 10-item DFI wound score		3–49
Range of total eight-item DFI wound score		3–43

ii.

^aEach assessed and placed in one of the pre-assigned categories. ^bFor the analysis of the SIDESTEP study data presented here, because there were few patients in the most severe group, some moderate scoring values were combined with the severe group. *Wound measurements:* Size (cm²), the ulcer area as traced with a fine-tipped felt pen on a sterile clear plastic film applied over the wound. Scored as shown (0–10) based on size of the ulcer (0 to > 30 cm²). Depth (mm), measured in the deepest apparent part of the wound using a sterile cotton-tipped wooden swab held 90° to the wound and marked with a pen held parallel to the surface of the intact skin. Undermining (mm), measurement of any tunneling, subepithelial tissue loss, or shearing, as measured using a sterile cotton-tipped wooden swab; scored as shown (3–8) based on the measured amount (< 2 mm to > 5 mm). *Wound parameters:* **Purulent drainage**, a viscous, yellowish-white or greenish fluid formed in infected tissue. **Nonpurulent drainage**, a serous, sanguineous, or serosanguineous collection of fluid in the tissue surrounding the wound. *Grade:* absent: none present; mild: scant drainage noted on dressing (< 0.5 cm diameter) not requiring additional dressings; moderate: greater than scant but less than copious drainage on dressing (> 2 cm diameter) requiring additional dressing changes; severe: copious drainage on dressing (> 2 cm diameter) requiring additional dressing changes. **Erythema**, congestive or exudative redness surrounding the wound caused by engorgement of the capillaries in the lower layers of the skin. *Grade:* none: absent; mild: pink, barely perceptible; moderate: pale red with defined edges; severe/extreme: red to dark red. **Induration**, inflammatory hardening or thickening of tissues; sometimes called "brawny edema." *Grade:* none: absent; mild: localized to the site of infection; moderate: limited extension from the site of infection; severe: extending from the site of infection to involve a substantial portion of the affected lower extremity. **Tenderness** (sign), palpation of the site of infection elicits a report by the patient of tenderness; measured on a 0 (no tenderness) to 10 (the worst imaginable tenderness) scale. *Grade:* none: absent; mild: score of ≤5; moderate: score of 6–8; severe: score of ≥9. **Pain** (symptom), subjective reporting of discomfort or the perception of pain at the site of the infection as reported by the patient; measured on a 0 (no pain) to 10 (the worst imaginable pain) scale. *Grade:* none: absent; mild: score of ≤5; Moderate: score of 6–8; Severe: score of ≥9. **Local warmth** (sign), Increase in skin temperature relative to the uninfected contralateral foot. *Grade:* none: temperature of the two sides the same; mild: temperature slightly, but perceptibly warmer; moderate: temperature clearly warmer (perceived as 1–2°F); severe: marked difference in temperature (perceived as > 2°F).

Table 3. i) 10 item DFI, ii) Details and explanation of DFI items.

Recently the Society for Vascular Surgery Lower Extremity Guidelines Committee undertook the task of creating a new classification of the threatened lower extremity. Risk stratification is based on three major factors that impact amputation risk and clinical management: Wound, Ischemia, and foot Infection (WIFI) (Table 4). ⁶⁸i.

W: Wound/clinical category
SVS grades for rest pain and wounds/tissue loss (ulcers and gangrene):
0 (ischemic rest pain, ischemia grade 3; no ulcer) 1 (mild) 2 (moderate) 3 (severe)

<i>Grade</i>	<i>Ulcer</i>	<i>Gangrene</i>
0	No ulcer	No gangrene
Clinical description: ischemic rest pain (requires typical symptoms + ischemia grade 3); no wound.		
1	Small, shallow ulcer(s) on distal leg or foot; no exposed bone, unless limited to distal phalanx	No gangrene
Clinical description: minor tissue loss. Salvageable with simple digital amputation (1 or 2 digits) or skin coverage.		
2	Deeper ulcer with exposed bone, joint or tendon; generally not involving the heel; shallow heel ulcer, without calcaneal involvement	Gangrenous changes limited to digits
Clinical description: major tissue loss salvageable with multiple (≥3) digital amputations or standard TMA ± skin coverage.		
3	Extensive, deep ulcer involving forefoot and/or midfoot; deep, full thickness heel ulcer ± calcaneal involvement	Extensive gangrene involving forefoot and /or midfoot; full thickness heel necrosis ± calcaneal involvement
Clinical description: extensive tissue loss salvageable only with a complex foot reconstruction or nontraditional TMA (Chopart or Lisfranc); flap coverage or complex wound management needed for large soft tissue defect		

TMA, Transmetatarsal amputation.

ii)

I: Ischemia

Hemodynamics/perfusion: Measure TP or TcPO₂ if ABI incompressible (>1.3)
SVS grades 0 (none), 1 (mild), 2 (moderate), and 3 (severe).

Grade	ABI	Ankle systolic pressure	TP, TcPO ₂
0	≥0.80	>100 mm Hg	≥60 mm Hg
1	0.6-0.79	70-100 mm Hg	40-59 mm Hg
2	0.4-0.59	50-70 mm Hg	30-39 mm Hg
3	≤0.39	<50 mm Hg	<30 mm Hg

ABI, Ankle-brachial index; PVR, pulse volume recording; SPP, skin perfusion pressure; TP, toe pressure; TcPO₂, transcutaneous oximetry. Patients with diabetes should have TP measurements. If arterial calcification precludes reliable ABI or TP measurements, ischemia should be documented by TcPO₂, SPP, or PVR. If TP and ABI measurements result in different grades, TP will be the primary determinant of ischemia grade. Flat or minimally pulsatile forefoot PVR = grade 3.

iii)

II: foot Infection:

SVS grades 0 (none), 1 (mild), 2 (moderate), and 3 (severe: limb and/or life-threatening)
SVS adaptation of Infectious Diseases Society of America (IDSA) and International Working Group on the Diabetic Foot (IWGDF) perfusion, extent/size, depth/tissue loss, infection, sensation (PEDIS) classifications of diabetic foot infection

Clinical manifestation of infection	SVS	IDSA/PEDIS infection severity
No symptoms or signs of infection	0	Uninfected
Infection present, as defined by the presence of at least 2 of the following items: <ul style="list-style-type: none"> • Local swelling or induration • Erythema >0.5 to ≤2 cm around the ulcer • Local tenderness or pain • Local warmth • Purulent discharge (thick, opaque to white, or sanguineous secretion) 	1	Mild
Local infection involving only the skin and the subcutaneous tissue (without involvement of deeper tissues and without systemic signs as described below). Exclude other causes of an inflammatory response of the skin (eg, trauma, gout, acute Charcot neuro-osteopathy, fracture, thrombosis, venous stasis)		

Clinical manifestation of infection	SVS	IDSA/PEDIS infection severity
Local infection (as described above) with erythema >2 cm, or involving structures deeper than skin and subcutaneous tissues (eg, abscess, osteomyelitis, septic arthritis, fasciitis), and No systemic inflammatory response signs (as described below)	2	Moderate
Local infection (as described above) with the signs of SIRS, as manifested by two or more of the following: <ul style="list-style-type: none"> • Temperature >38° or <36°C • Heart rate >90 beats/min • Respiratory rate >20 breaths/min or PaCO₂ <32 mm Hg • White blood cell count >12,000 or <4000 cu/mm or 10% immature (band) forms 	3	Severe ^a

PACO₂, Partial pressure of arterial carbon dioxide; SIRS, systemic inflammatory response syndrome.

^aIschemia may complicate and increase the severity of any infection. Systemic infection may sometimes manifest with other clinical findings, such as hypotension, confusion, vomiting, or evidence of metabolic disturbances, such as acidosis, severe hyperglycemia, new-onset azotemia.

Table 4. i) Wound score. ii) Ischemia score. iii) foot infection score.

One more classification system to categorize and define diabetic ulcer objectively and facilitate communication between health-care providers, was developed by the IWGDF. Diabetic ulcers are classified according to five categories: perfusion, extent/size, depth/tissue loss, infection and sensation; the Perfusion, Extent, Depth, Infection and Sensation (PEDIS) classification system (which is mentioned in table 4).⁶⁹

6. Strategy for diabetic foot ulcer management

The IWGDF had previously published practical guidelines for the prevention and management of diabetic foot ulcer in 2011,^{36,56} and recently the IWGDF Editorial Board produced an updated summary guidance for daily practice. The resultant of this process, after review by the Editorial Board and by international IWGDF members of all documents, is an evidence-based global consensus on prevention and management of foot problems in diabetes.⁷⁰

Nowadays, it has been clear that diabetic foot ulcer is a matter of a multidisciplinary team that should be consisted by a number of specialists such diabetologist, vascular surgeon, orthopedic surgeon, general

surgeon, dermatologist, specialized nurse, psychologist and every physicians that could help in the diabetic foot treatment.

6.1 Principles of ulcer treatment

6.1.1 Pressure relief and protection of the ulcer

- Mechanical off-loading – the cornerstone in ulcers with increased biomechanical stress
- Total contact casting or other casting techniques – preferable in the management of plantar ulcers
- Temporary footwear
- Individually moulded insoles and fitted shoes
- Non-weight bearing
- limitation of standing and walking crutches, etc.

6.1.2 Restoration of skin perfusion

- Peripheral arterial disease is the most important factor relating to the outcome of a diabetic foot ulcer. Healing will be severely

impaired in diabetic patients with a foot ulcer in case of symptoms or signs of ischemia, and a low ABPI or TBI.

- The benefits of pharmacological treatment to improve perfusion have not been established.
- Emphasis should be placed on cardiovascular risk reduction (cessation of smoking, treatment of hypertension and dyslipidaemia, use of aspirin).

However there is still debate on if someone has always to revascularize patients with diabetic ulcer with open procedure or endovascular one or even treat them conservatively. In a recent systematic review studies appeared to demonstrate improved rates of limb salvage associated with revascularization compared with the results of conservatively treated patients in the literature. Nevertheless, there were insufficient data to recommend one method of revascularization over another.⁷¹

There are also supporters of the direct revascularization according the angiosomes concept. Briefly, the foot can be divided into six angiosomes (Figure 12): three arising from the posterior tibial artery, one from the anterior tibial artery, and two from the peroneal artery. The anterior tibial artery supplies the dorsal side of the toe and

dorsal foot; the posterior tibial artery supplies the plantar side of the toe, web space of the toes, plantar foot, and the inside of the heel; and the peroneal artery supplies lateral ankle and the outside of the heel. For intervention, we first confirmed the location of nonhealing ulceration/gangrene and the angiosome-based favorable target lesion by digital subtraction angiography and then we are undertaking the procedure.⁷²

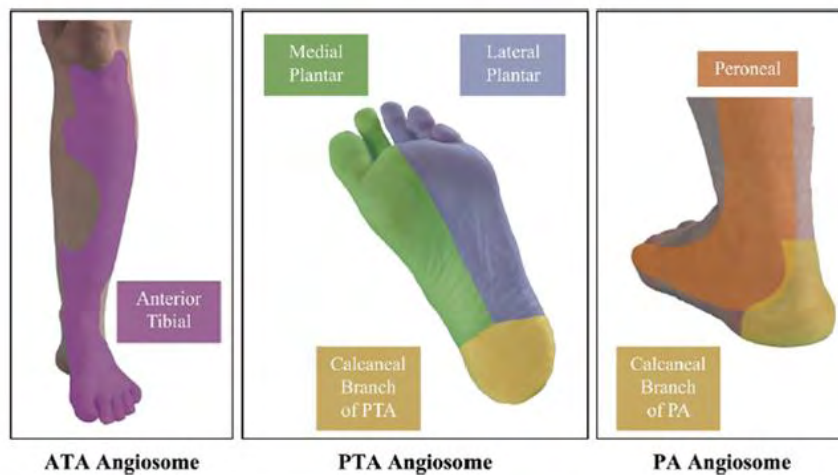


Figure 12. The foot can be divided into six angiosomes: three arising from the posterior tibial artery, one from the anterior tibial artery, and two from the peroneal artery.

However, there is always the conservative treatment even for revascularization. There are diabetic patients with ischemic foot ulcers not available for revascularizations that are not though excluded from healing without major amputation.⁷³

6.1.3 Treatment of infection

- Superficial ulcer with skin infection
 - ❖ Cleanse, debride all necrotic tissue and surrounding callus
 - ❖ Start empiric oral antibiotic therapy targeted at S.aureus and streptococci.

- Deep (potentially limb-threatening) infection
 - ❖ Urgently evaluate for surgical drainage to remove necrotic tissue, including infected bone, and drain abscesses
 - ❖ Consider need for arterial revascularization
 - ❖ Initiate empiric, parenteral broad-spectrum antibiotic therapy aimed at Gram-positive and Gram-negative bacteria, including anaerobes.

- Metabolic control and treatment of co morbidities.

- ❖ Optimal diabetes control, if necessary with insulin (blood glucose <8 mmol/L or <140mg/dL)
- ❖ Treatment of edema and malnutrition
- Local wound care
- ❖ Frequent wound inspection
- ❖ Frequent wound debridement (with scalpel)
- ❖ Control of exudation and maintenance of moist environment
- ❖ Consideration of negative pressure therapy in postoperative wounds
- There are treatments which are not established in routine management:
 - ❖ Biological active products (collagen, growth factors, bio-engineered tissue) in neuropathic ulcers
 - ❖ Systemic hyperbaric oxygen treatment
 - ❖ Silver or other anti-microbial agents containing dressings

6.1.4 Education of patients and their social environment

Instruction should be given on appropriate self-care and on how to recognize and report signs and symptoms of (worsening) infection such

as fever, changes in local wound conditions, or hyperglycemia. Both group and individual training approaches could increase foot care self-efficacy in the patients with DM.⁷⁴

6.1.5 Determining the cause and preventing recurrence

The cause of the ulceration should be determined in order to reduce the chance of recurrences. Ulcers on contra-lateral foot should be prevented and heel protection provided during periods of bed rest. Once the episode is over, the patient should be included in a comprehensive foot care program with life-long observation.

7. Psychosocial implication and quality of life in patients with diabetic foot ulcer

During last decade the medical society has been focused on the social-economical and psychological impact of diabetic foot ulcer on patients. Along with increased morbidity, foot ulcers can lead to lifelong disability and may substantially diminish the quality of life (QOL) for these patients.⁷⁵ Specifically, patients with diabetic foot ulcers have restrictions on mobility, poor psychosocial adjustment, and lower self-

perceptions of health than patients who do not have ulcers.^{75,76} An understanding of the specific effects of chronic diabetic foot ulcers on individual patients' QOL is central to the direction of treatment, management of compliance, and patient/practitioner communication. Brod et al.⁷⁵ conducted focus groups with patients with foot ulcers and reported that ulcers had a negative impact on almost every aspect of QOL, including psychological, physical, social and economic functioning. For example, approximately 50% of patients indicated that they were no longer employed because of their foot ulcers, and many patients reported that their dependence on others placed a strain on their relationships with members.

The Diabetic Foot Ulcer Scale (DFS) was developed to measure the impact of diabetic foot ulcers on QOL issues most important to patients. The DFS was also translated into several languages using both forward and backward translations and cognitive debriefing to ensure cultural equivalence. The DFS contains a total of 64 items, 58 of which are used to compute 15 QOL subscales.⁷⁷ The six remaining items address employment-related issues and are not included in computation of subscale scores on the DFS long form.

The final version of the DFS-SF (short-form)⁷⁸ which is used broadly contains a total of 29 items grouped into six subscales:

- Leisure (5 items)
- Physical health (5 items)
- Dependence/daily life (5 items)
- Negative emotions (6 items)
- Worried about ulcers/feet (4 items)
- Bothered by ulcer care (4 items)

Scale	Item number	Meaning of scores	
		Low	High
Leisure	1a	1 = "My foot ulcer problems stopped me a great deal from doing the hobbies and recreational activities that I enjoy"	5 = "My foot ulcer problems did not at all stop me from doing the hobbies and recreational activities that I enjoy"
	1b	1 = "My foot ulcer problems changed a great deal the kinds of hobbies and recreational activities that I enjoy"	5 = "My foot ulcer problems did not at all change the kinds of hobbies and recreational activities that I enjoy"
	1c	1 = "My foot ulcer problems stopped me a great deal from getting away for a holiday or a weekend break"	5 = "My foot ulcer problems did not at all stop me from getting away for a holiday or a weekend break"
	1d	1 = "My foot ulcer problems made me a great deal choose a different kind of holiday or short break than I would have preferred"	5 = "My foot ulcer problems did not at all make me choose a different kind of holiday or short break than I would have preferred"
	1e	1 = "My foot ulcer problems meant a great deal that I had to spend more time planning and organizing for leisure activities"	5 = "My foot ulcer problems did not at all mean that I had to spend more time planning and organizing for leisure activities"
Physical health	2a	1 = "Because of my foot ulcer problems, I feel all of the time fatigued or tired"	5 = "Because of my foot ulcer, I feel none of the time fatigued or tired"
	2b	1 = "Because of my foot ulcer problems, I feel all of the time drained"	5 = "Because of my foot ulcer problems, I feel none of the time drained"
	2c	1 = "Because of my foot ulcer problems, I feel all of the time that I have difficulty sleeping"	5 = "Because of my foot ulcer problems, I feel none of the time that I have difficulty sleeping"

Scale	Item number	Meaning of scores	
		Low	High
	2d	1 = "Because of my foot ulcer problems, I feel all of the time pain while walking or standing"	5 = "Because of my foot ulcer problems, I feel none of the time pain while walking or standing"
	2e	1 = "Because of my foot ulcer problems, I feel all of the time pain during the night"	5 = "Because of my foot ulcer problems, I feel none of the time pain during the night"
Dependence / daily life	3a	1 = "Because of my foot ulcer problems, I have all of the time to depend on others to help me look after myself (such as washing and dressing myself)"	5 = "Because of my foot ulcer problems, I have none of the time to depend on others to help me look after myself (such as washing and dressing myself)"
	3b	1 = "Because of my foot ulcer problems, I have all of the time to depend on others to do household chores such as cooking, cleaning or laundry"	5 = "Because of my foot ulcer problems, I have none of the time to depend on others to do household chores such as cooking, cleaning or laundry"
	3c	1 = "Because of my foot ulcer problems, I have all of the time to depend on others to get out of the house"	5 = "Because of my foot ulcer problems, I have none of the time to depend on others to get out of the house"
	3d	1 = "Because of my foot ulcer problems, I have all of the time to spend more time planning or organizing my daily life"	5 = "Because of my foot ulcer problems, I have none of the time to spend more time planning or organizing my daily life"
	3e	1 = "Because of my foot ulcer problems, I feel all of the time that doing anything takes longer than I would have liked"	5 = "Because of my foot ulcer problems, I feel none of the time that doing anything takes longer than I would have liked"
Negative emotions	4a	1 = "Because of my foot ulcer problems, I feel extremely angry because I am not able to do what I	5 = "Because of my foot ulcer problems, I feel not at all angry because I am not able to do what I want to do"

Scale	Item number	Meaning of scores	
		Low	High
		want to do"	
	4b	1 = "Because of my foot ulcer problems, I feel extremely frustrated by others doing things for me when I would rather do them myself"	5 = "Because of my foot ulcer problems, I feel not at all frustrated by others doing things for me when I would rather do them myself"
	4c	1 = "Because of my foot ulcer problems, I feel extremely frustrated because I am not able to do what I want to do"	5 = "Because of my foot ulcer problems, I feel not at all frustrated because I am not able to do what I want to do"
	4g	1 = "Because of my foot ulcer problems, I feel extremely worried that my ulcer(s) will never heal"	5 = "Because of my foot ulcer problems, I feel not at all worried that my ulcer(s) will never heal"
	4i	1 = "Because of my foot ulcer problems, I feel extremely worried that I may have an amputation"	5 = "Because of my foot ulcer problems, I feel not at all worried that I may have an amputation"
	4j	1 = "Because of my foot ulcer problems, I feel extremely frustrated because I have difficulty in getting about"	5 = "Because of my foot ulcer problems, I do not at all feel frustrated because I have difficulty in getting about"
Worried about ulcers / feet	4d	1 = "Because of my foot ulcer problems, I feel extremely worried that my ulcer(s) will never heal"	5 = "Because of my foot ulcer problems, I feel not at all worried that my ulcer(s) will never heal"
	4e	1 = "Because of my foot ulcer problems, I feel extremely worried that I may have an amputation"	5 = "Because of my foot ulcer problems, I feel not at all worried that I may have an amputation"
	4f	1 = "Because of my foot ulcer problems, I feel extremely worried about injury to my feet"	5 = "Because of my foot ulcer problems, I feel not at all worried about injury to my feet"

Scale	Item number	Meaning of scores	
		Low	High
	4h	1 = "Because of my foot ulcer problems, I feel extremely worried about getting ulcers in the future"	5 = "Because of my foot ulcer problems, I feel not at all worried about getting ulcers in the future"
Bothered by ulcer care	5a	1 = "Because of my foot ulcer problems, I am all of the time bothered by having to keep the weight off my foot ulcer"	5 = "Because of my foot ulcer problems, I am None of the time bothered by having to keep the weight off my foot ulcer"
	5b	1 = "Because of my foot ulcer problems, I am all of the time bothered by the amount of time involved in caring for my foot ulcer (including dressing changes, waiting for the district nurse and keeping the ulcer clean)"	5 = "Because of my foot ulcer problems, I am none of the time bothered by the amount of time involved in caring for my foot ulcer (including dressing changes, waiting for the district nurse and keeping the ulcer clean)"
	5c	1 = "Because of my foot ulcer problems, I am all of the time bothered by the appearance, odour or leaking of my ulcer"	5 = "Because of my foot ulcer problems, I am none of the time bothered by the appearance, odour or leaking of my ulcer"
	5d	1 = "Because of my foot ulcer problems, I am all of the time bothered by having to depend on others to help me care for my foot ulcer"	5 = "Because of my foot ulcer problems, I am none of the time bothered by having to depend on others to help me care for my foot ulcer"

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Part B

1. Aim of the study

Primary aim:

To assess the impact of various associated factors on the healing process in diabetic foot ulcers.

Secondary aims:

- i. To conduct a survey in order to highlight the current trends in the management of diabetic foot among Vascular Specialists practicing in the Mediterranean region.

- ii. To apply the Greek version of the LANSS questionnaire on patients with diagnosed neuropathic pain, to assess its validity and investigate any association of LANNS with visual analog pain scales (VAS-ADL; activities of daily living and VAS-INT; pain intensity).

iii. To apply the WiFi and 10-item DFI classification systems and correlate them with any other factor which is associated with wound healing and limb loss.

iv. To apply the Diabetic Foot Ulcer Scale Short form of the Greek version which was developed to measure the impact of diabetic foot ulcers on QOL issues most important to patients.

2. Methodology

An observational study of 103 diabetic patients with foot ulcer being followed up for 12 months.

INCLUSION CRITERIA

- DM type 2
- Foot ulcer
- Age > 18 years

EXCLUSION CRITERIA

- Malnutrition (BMI < 18)
- Immobility (bed or wheel chair bound or stroke limb)
- Pharmaceutical immune-suppression (steroids or recently transplantation)
- Patient without disposing capacity in their past medical history (such as schizophrenia, Alzheimer disease, et al)

- Unable to read and write Greek

A common protocol was completed for every patient during first examination.

- Date of first examination and every other one that followed.
- The place that they live (city, suburbs or village).The occupation that they have (labor or office work) and what is their supporting family environment.
- The Body mass index (BMI), their height and weight.
- The level of self care such as:
 - Self examination times per week
 - Foot washing times per week
 - Foot hydration times per week
 - Cutting their nails
 - If they wear any special shoes
 - If they walk barefoot
- Which doctor referred him to our department , how many times , and to which other specialties
- Time interval between the ulcer and the referral

- Cause of ulcer (shoe trauma, cutting nails trauma, unknown, other cause)
- History of claudication, previous ulcer, previous vascular intervention, previous amputation.
- Family history of coronary artery disease (CAD), DM and PAD
- Texas Wound Classification of the ulcer
- 10-items DFI classification of the ulcer
- WiFi classification of the ulcer
- Past medical history of hypertension (HT), hyperlipidemia (HL), CAD, atrial fibrillation (AF), DM and its duration, chronic renal disease (CRD), chronic obstructive pulmonary disease (COPD), cerebro-vascular disease (CVD), alcohol or tobacco use. Whether the patient has stopped or restarted smoking.
- If the patient is on antiplatelet, statin, insulin, other medication for DM, vitamin K antagonist or any new oral anticoagulants.
- Blood tests:
Haematocrit (Hct), Haemoglobin (Hb), White blood cells (Wbc) and their type (Neutrophilic or Lymphocytes), platelets

(PLT) number, mean platelet volume (MPV), Erythrocyte Sedimentation Rate (ESR), c-reactive protein (CRP), creatinine (CR), Urea (Ur), sodium (Na) and potassium (K), Aspartate Aminotransferase (AST or SGOT), Alanine Aminotransferase (ALT or SGPT), Creatine phosphokinase (CPK), lactate dehydrogenase (LDH), Billirubin (direct/indirect) , International Normalized Ratio (INR) , Prothrombin time (PT) , partial thromboplasmin time (APTT), low density lipoprotein (LDL) , high density lipoprotein (HDL) , Cholesterol , triglycerides, HbA1c (hemoglobin A1c test).

- Clinical examination with palpable pulses of femoral, popliteal, posterior tibial and dorsalis pedis arteries and ABPI
- Antibiotics therapy
- Cultures from the ulcer
- LANSS scale of each patient
- VAS ADL and VAS INT
- Imaging with foot X-ray, DSA (angiograms that are related with the ulcer), CTA or MRA
- Any minor or major amputation

- Vascular intervention open or endovascular one
- Post-op ABPI
- Any new medication
- Any new referral to other specialty
- Completion of Diabetic Foot Ulcer Scale Short form of the Greek version.

During re-examination, a re-evaluation of each patient was undertaken and an individualized re-examination was decided afterwards.

Primary Outcomes:

- Healed ulcer during 12 months
- Unhealed ulcer during 12 months
- Major or minor amputation during 12 months
- Death during 12 months

Additionally:

- A survey with SurveyMonkey (<https://www.surveymonkey.com/>) was conducted from December 2013 to November 2014, including 10 main questions on the management of diabetic foot patients. The

questionnaire was sent to Vascular Specialists included in the current mailing list of the Mediterranean League of Angiology and Vascular Surgery. Spearman's correlation analysis was used for statistical analysis. This section is explained thoroughly in the published paper which is part of the results.

- A prospective instrument validation study of LANSS was conducted in University Hospital of Larissa, on 70 patients (35 NP and 35 nociceptive pain), from April 2015-June 2015. Visual analog pain scales (VAS-ADL; impact of pain on daily living activities, VAS-INT; pain intensity) were also assessed and correlated with LANSS scale. This section is explained thoroughly in the published paper which is part of the results.
- The Diabetic Foot Ulcer Scale Short form of the Greek version was answered by 103 diabetic patients that were treated in our department. Every patient answered this form during the first examination with the presence of foot ulcer, and then they answered after either the healed ulcer or the minor amputation or the major amputation or after a year even with their ulcer unhealed.

Part C

• Publications:

I. Spanos K, Lachanas V, Karathanos C, Poredos P, Hussein E, Giannoukas AD. A survey on the status of the management of diabetic foot in the Mediterranean region. *Int Angiol.* 2015 Feb 13. [Epub ahead of print]

A survey on the status of the management of diabetic foot in the Mediterranean region

Original Article

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This survey was undertaken under the auspices of Mediterranean League of Angiology and Vascular Surgery (MLAVS)

ABSTRACT

Aim: We conducted a survey in order to highlight the current trends in the management of diabetic foot among Vascular Specialists practicing in the Mediterranean region.

Methods: A survey Monkey was conducted from December 2013 to November 2014, including 10 main questions on the management of diabetic foot patients. The questionnaire was sent to Vascular Specialists included in the current mailing list of the Mediterranean League of Angiology and Vascular Surgery. Spearman's correlation analysis was used for statistical analysis.

Results: The response rate was 37.5% (150/400) and 52.6% of them were practicing in a Tertiary hospital service. The diabetic foot patient management and most of the amputations were performed in Tertiary hospitals. Most responders were experienced vascular specialists (55.3%). In general specialists with high work volume performed more major amputations in diabetic patients as compared to PAD patients and adopted equally all types of interventions (open, endovascular and hybrid). In particular the most experienced specialists required more diagnostic investigations, performed more minor amputations and used endovascular approach as first line treatment in diabetic patients. A lack

of multidisciplinary approach was demonstrated as referral to other specialties was suboptimal.

Conclusion: In the Mediterranean region, patients with diabetic foot are managed by the most experienced vascular physicians in Tertiary centers. Endovascular first approach seems to be the preferred strategy, but services were able to provide open as well as hybrid procedures. Finally, the multidisciplinary team approach has not been adopted as part of the standard care even in tertiary centers.

Key words: Diabetic foot, multidisciplinary team, amputation.

Introduction

Foot infection in patients with diabetes mellitus (DM) remains an important issue with chronic and highly disabling complications associated with high risk of limb loss.¹

The most common presentation of diabetic foot infections (DFIs) usually is associated with an ulcer that occurs from trauma as a consequence of peripheral sensory and motor neuropathy. Various microorganisms inevitably colonize the wound and very often one or more species grow in the wound, which may lead to tissue damage and inflammation.²DFIs impose a major economic burden and cost is increased disproportionately to the severity of the condition. The treatment of DM and its complications in the United States generated at least \$116 billion in direct costs of which at least 1/3 of them were linked to the treatment of DFIs.³ Additionally, DFI is the leading cause of non-traumatic lower limb amputations in the world, resulting in an amputation risk that is approximately 40 times greater than that of the general population² and most of them are preceded by foot ulceration.⁴ Thus, prevention and treatment strategies of DFIs are of paramount importance. However, there is lack of nation-wide formal primary care-based diabetic foot service around the world, and focused research is still needed to

confirm that such service in the diabetic community is effective in terms of prevention and cost-effectiveness.⁵

As far as the treatment of DFIs is concerned, selective revascularization strategies are advocated, either using open procedures as the initial approach or endovascular therapies that have acquired an important role in current practice with promising results.^{6,7,8} However, treatment of many patients is not in line with current guidelines and there is a wide variation among countries and centers. The Eurodiale study suggested that guidelines were too general and that healthcare organizational barriers and personal perceptions resulted in underuse of recommended therapies.⁹

This survey was conducted under the guidance of the Mediterranean League of Angiology and Vascular Surgery (MLAVS) to highlight what are the current trends in the management of diabetic foot in the Mediterranean region.

Methodology

An internet survey using Survey Monkey system¹⁰, which is an online survey software, was conducted. A questionnaire (Table 1) having 10 questions covered the following domains; domain 1: physicians'

related practice (questions 1,2), domain 2: physicians' clinical practise (questions 3,4,5,6), domain 3: physicians' treatment methods (questions 7,8,9), domain 4: physicians' co-operation with other specialties (questions 10). Question 3 was divided in 3 sub-questions depending on the type of pathology treated by the individual physician. Likewise question 9 was further divided in 3 sub-questions depending on intervention used in the treatment (open, endovascular or hybrid).

The questionnaire was sent through the mailing list of the MLAVS. Invitation was send to vascular specialists practicing in Mediterranean and Southern European countries (Egypt, Italy, Lebanon, Portugal, Serbia, France, Greece, Bulgaria, Cyprus, Romania, Croatia, Slovenia, Algeria, Turkey, Israel and Tunisia). The period of survey was 12 months (from 12.2013 to 11.2014). After the first invitation, nine more reminders were sent in order to raise the attention of interested physicians and to achieve a decent response rate. Data was extracted by the software of the service of Survey Monkey. Spearman's correlation analysis was performed by using the SPSS 20 statistical software (IBM, Chicago, IL, USA). P values lower than 0.05 were considered as statistically significant.

Results

The questionnaire was sent to 400 vascular specialists. The response rate was 37.5% (150/400). The vast majority of responders were experienced vascular specialists practicing for more than 25 years in the field (55.3%) (Figure 1). About half of participants were practicing in a Tertiary centre (University hospital service, 52.6 %), while the remaining ones were practicing in various types of hospital (regional, general or private) (Figure 2).

Spearman's correlation coefficient rho (r_s) showed that, hospital type was correlated significantly with: the management of both diabetic ($r_s=.202$, $p < 0.05$) and non-diabetic PAD patients ($r_s=.240$, $p < 0.01$), and with amputation rate (minor [$r_s=.340$, $p < 0.01$] and major [$r_s=.335$, $p < 0.05$]). More specifically, University Hospitals dealt with more patients (diabetic and non-diabetic) and undertook more amputations.

The experience of the vascular specialists was significantly correlated with the management of patients with critical limb ischaemia (CLI) ($r_s=.260$, $p < 0.01$), vascular investigations ($r_s=.162$, $p < 0.05$), minor amputations ($r_s=.208$, $p < 0.05$) and endovascular interventions ($r_s=.187$, $p < 0.05$) in diabetic patients. Along these lines, specialists with experience more than 25 years, handled more CLI patients, requested more vascular investigations for the diagnosis of diabetic patient,

proceeded in more minor amputations and preferred endovascular interventions as first line treatment approach.

As it is showed on figure 3, the specialist had to manage diabetic patients with more complicated clinical presentation, such as diabetic neuropathy (74.15%), gangrene (52.38%) and ulcer (46.94%).

Furthermore, specialists that were treating higher number of diabetic patients, performed more major amputations ($r_s=.278$, $p<0.01$) and used all the armament of interventions (open [$r_s=.335$, $p<0.01$], endovascular [$r_s=.314$, $p<0.01$] or hybrid [$r_s=.282$, $p<0.01$]).

In the diagnosis, specialists used mostly duplex scan (70.95%), Ankle Brachial Index (ABPI, 51.35%) or Digital Subtraction Angiography (DSA, 50.68%), (Figure 4). Physicians who requested more diagnostic investigations, were those who routinely examined less the patient for the presence of foot neuropathy before the intervention ($r_s=-.173$, $p < 0.05$). Indeed, only 60% (86/146) of the vascular specialists considered important to evaluate the diabetic foot for the presence of neuropathy before the treatment.

Those vascular specialists opting either endovascular first or open first approach were dealing in their services with the wide spectrum of vascular patients including diabetic and non-diabetic. Physicians in favor of endovascular first approach as treatment option performed more minor

($r_s=.343$, $p < 0.01$) and major ($r_s=.398$, $p < 0.01$) amputations, as compared to the ones in favor of open interventions who performed only major amputations but at a lower percentage ($r_s=.228$, $p < 0.05$). Vascular specialists who used hybrid procedures performed low numbers of amputation (minor or major).

Finally, the multidisciplinary approach model to patients with diabetic foot was poor as it is displayed in figure 5. The specialists tended to refer their patients to a Cardiologist in 68.09%), to a rehabilitation centre in 46.81%, while referral to ophthalmologist, podiatrist, dermatologist and physiotherapist was not part of the routine in the standard daily practice.

Discussion

Over the last 30 years, consensus documents have been produced and practical guidelines have been published for the management of diabetic foot both in National and Worldwide level.^{1,2,11,12,13,14,15} The St. Vincent Declaration was the first attempt in 1989 to set targets for the treatment of diabetic patients and the quality level of diabetes care in Europe.¹¹ Recently the Infectious Diseases Society of America (IDSA) in USA,² the Italian Societies of Diabetes in Europe¹ and the International Working Group on the Diabetic Foot (IWGDF) worldwide¹⁴ have

published updated practical guidelines for the diabetic foot management. Thus, while the multidisciplinary approach in the treatment is required the organization of such service is still unsettled in daily clinical practice. Along this line, we decided with our survey to highlight what is the current status in the management of diabetic foot in the Mediterranean region.

There is a geographic variation in the management of diabetic patients and their amputation rates are related to regional differences in the utilization of inpatient services.¹⁶ In our survey, most of the amputations were performed in tertiary hospitals, probably because diabetic foot is by far one of the worse complications in diabetic patients requiring dedicated vascular services that may not be available in small size hospitals in the Mediterranean region.¹⁷ This is supported further by the fact that even in the tertiary hospitals specialists involved with the treatment of diabetic foot were more experienced among their colleagues.

The other important trend that was demonstrated in our survey, was the fact that the senior specialists with >25 years of experience, preferred endovascular approach as first option for revascularizing the diabetic foot. This strategy has been adopted from various centers as a reasonable one regardless the degree of vascular pathology because of these patients' co-morbidities.¹⁸ However, vascular services involved in the management

of diabetic foot patients had expertise in both endovascular and surgical skills (open, endovascular and hybrid). It is of note that in our survey hybrid procedures were associated with lower rate of amputations. This is supported by several recent publications which present optimistic and positive results of hybrid procedures in the management of critical limb ischemia.^{17,19, 20,21} This reiterates that vascular services treating diabetic foot should be able to apply all types of interventions to optimize the outcomes.^{6,21}

In our survey, the first line diagnostic approach was duplex scan, followed by ABPI and DSA while useful diagnostic tools, such as toe-brachial pressure index (TBI) and the TcPO, in this category of patients who have uncompressible arteries, were scarcely implemented. While ABI has been recognized as a powerful tool for the detection of peripheral arterial disease not only in most epidemiological studies but also in diabetic patients^{22,23,24} surprisingly it was underused by the vascular specialists responded to our survey. This practice contradicts with the IWGDF guidelines¹⁷ that suggest in addition to a thorough assessment of history for symptoms of arterial insufficiency, all patients with a diabetic foot ulcer should undergo hand-held Doppler evaluation of both pedal pulses, measurement of ABI and, in cases of diagnostic

uncertainty, measurement of toe-brachial index (TBI) or transcutaneous pressure of oxygen (TcPO₂).¹⁷

The other noticeable finding in our survey, was that only 60% of the Vascular physicians considered as important to evaluate the patients with a diabetic foot for the presence of peripheral neuropathy before the treatment, although it is known that this can predict the risk of developing a diabetic foot ulcer or higher rate of amputation.²⁵

Finally, in our survey it was demonstrated that most of the vascular physicians had not adopted a multidisciplinary approach in the management of patients with diabetic foot as a routine in daily practice. The referral to Cardiologist was at the level of 60% but it was not within the standard strategy to seek advice from a podiatrist, ophthalmologist, physiotherapist and in case of amputation to refer the patient for rehabilitation. This finding shows clearly that at least in the Mediterranean region the multidisciplinary approach of diabetic foot patients is not part of the standard care, despite the fact that this type of approach can result in significant reductions in total and major amputations rates.^{26,27} Therefore, it appears that reorganization of the service provided to diabetic patients is of paramount importance in the healthcare system of the Mediterranean countries.

Finally, it should be acknowledged that our study may be inherent of some potential limitations. Firstly the response rate was 37.5%, which means that our results may not absolutely representative for the entire Mediterranean region. This is aggravated by the fact that our results were not analyzed with regard to the national origin of the physicians. Also, we considered for granted that all patients were under the care of an endocrine-internal medicine physician. Nevertheless, besides these limitations, we still think that our survey provides a valuable snapshot on the current status regarding the management of diabetic foot patients in the Mediterranean region and our findings reiterate those reported in several other studies.^{1,2,4,7,8,9,17,18,19,20,21}

Conclusion

In the Mediterranean region, patients with diabetic foot are managed by the most experienced vascular physicians in Tertiary centers. Endovascular first approach seems to be the preferred strategy, but services were able to provide open as well as hybrid procedures. Finally, the multidisciplinary team approach has not been adopted as part of the standard care even in tertiary centers.

Conflict of interest

None

Question 1	In what kind of hospital do you work?
Question 2	What is your clinical experience?
Question 3	What kind and how many patients do you treat per months?: (more than one answers)
Question 4	What is the most usual pathology of the diabetic patients in your Department?: (more than one answers)
Question 5	What is (are) your preferable vascular investigation(s) before intervention in diabetic patients with ulcer?: (more than one answers)
Question 6	Do you evaluate routinely the presence and the severity of neuropathy?:
Question 7	How many minor amputations do you perform every year per 100 treated diabetic patients?
Question 8	How many major amputations in diabetic patients do you perform every year?
Question 9	What is the method of your preference to revascularize patients with ischemic diabetic foot?: (more than one answers)
Question 10	Do you refer the patients routinely to a: (more than one answers)

Table 1. Survey Monkey Questions.

Figure 1. Question 2.

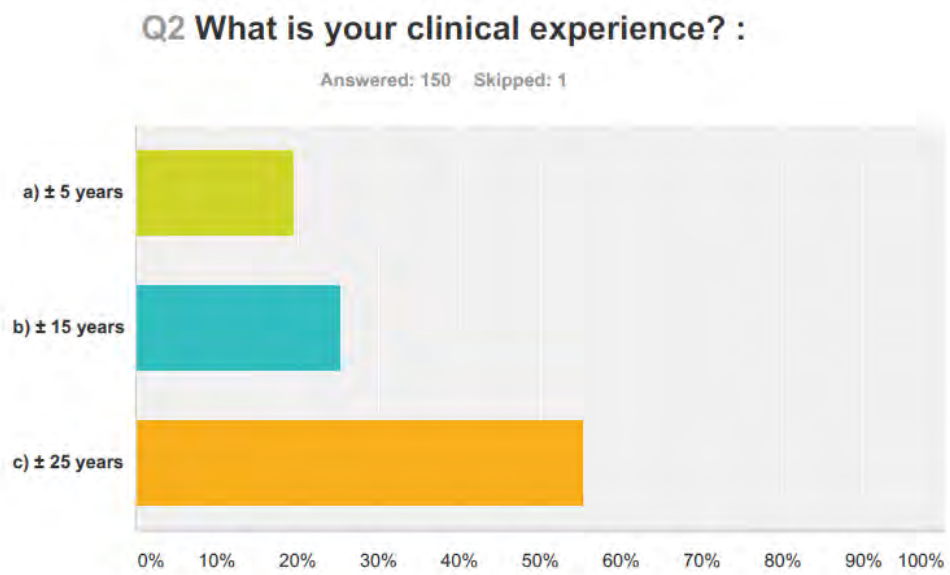


Figure 2. Question 1

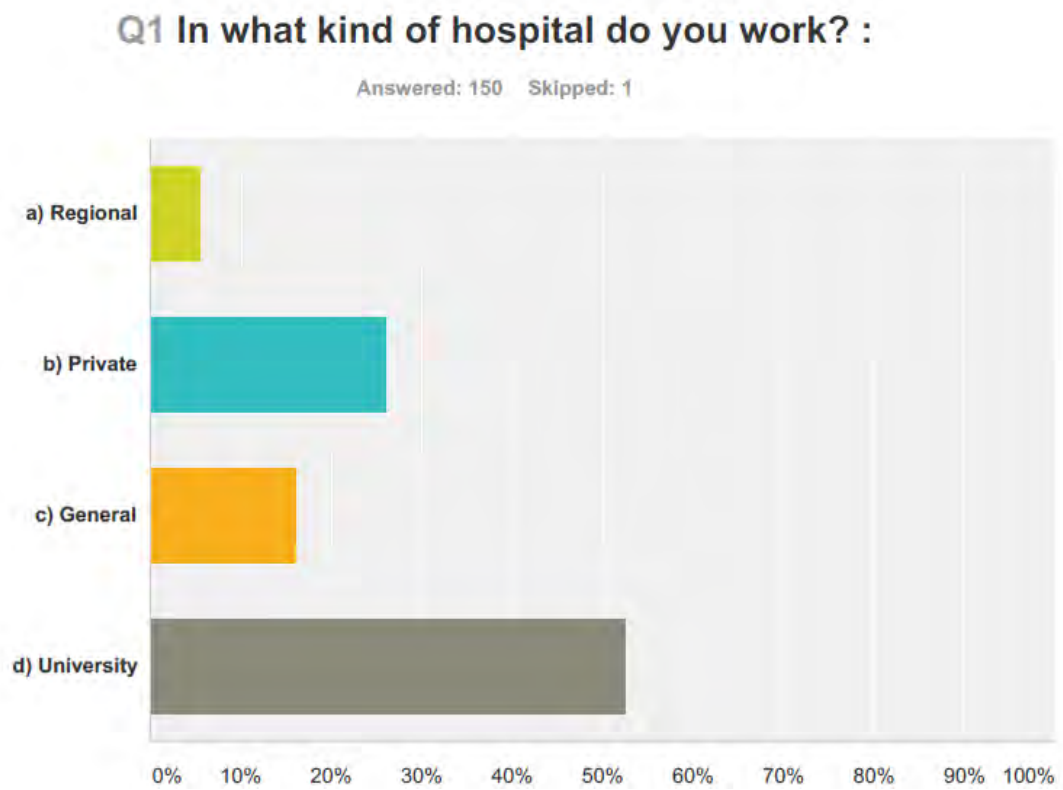


Figure 3. Question 4 (Diabetic vasculopathy: Diabetic vasculopathy with or without ulcer, pain without skin: pain without skin lesion)

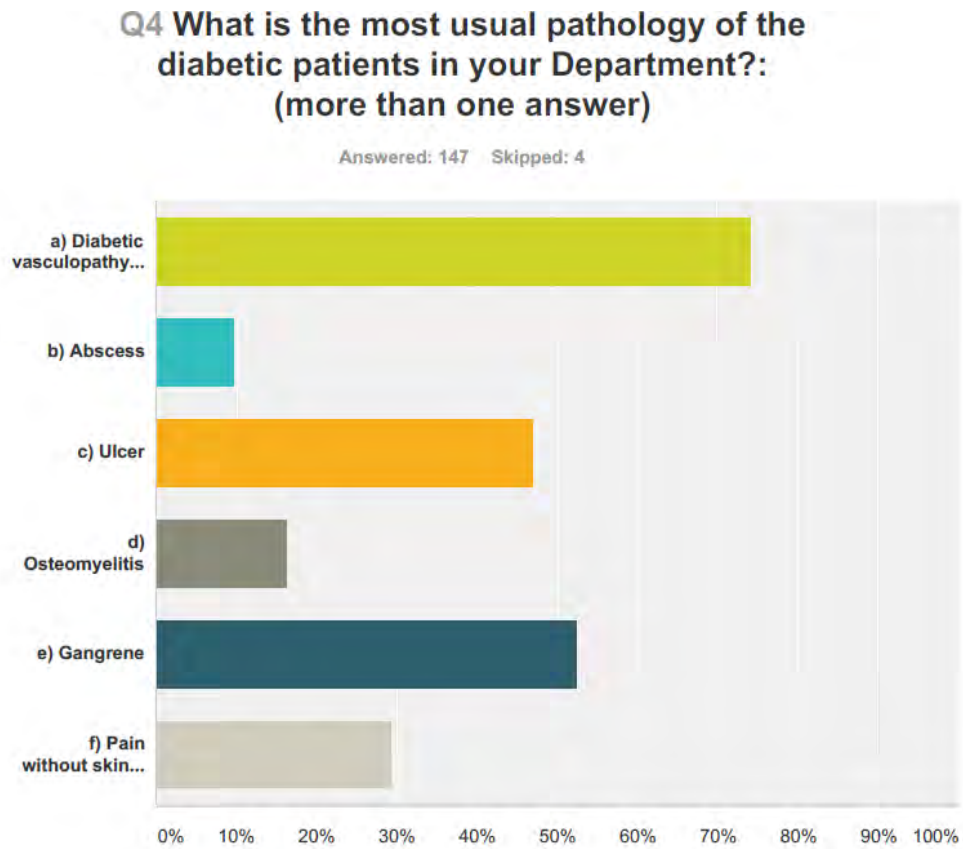


Figure 4. Question 5 (Toe-brachial: Toe-brachial index, Ankle brachial: Ankle brachial index, TCPO₂ : transcutaneous oxygen pressure, CTA: computed tomography angiography, MRA: magnetic resonance angiography, DSA: digital subtraction angiography)

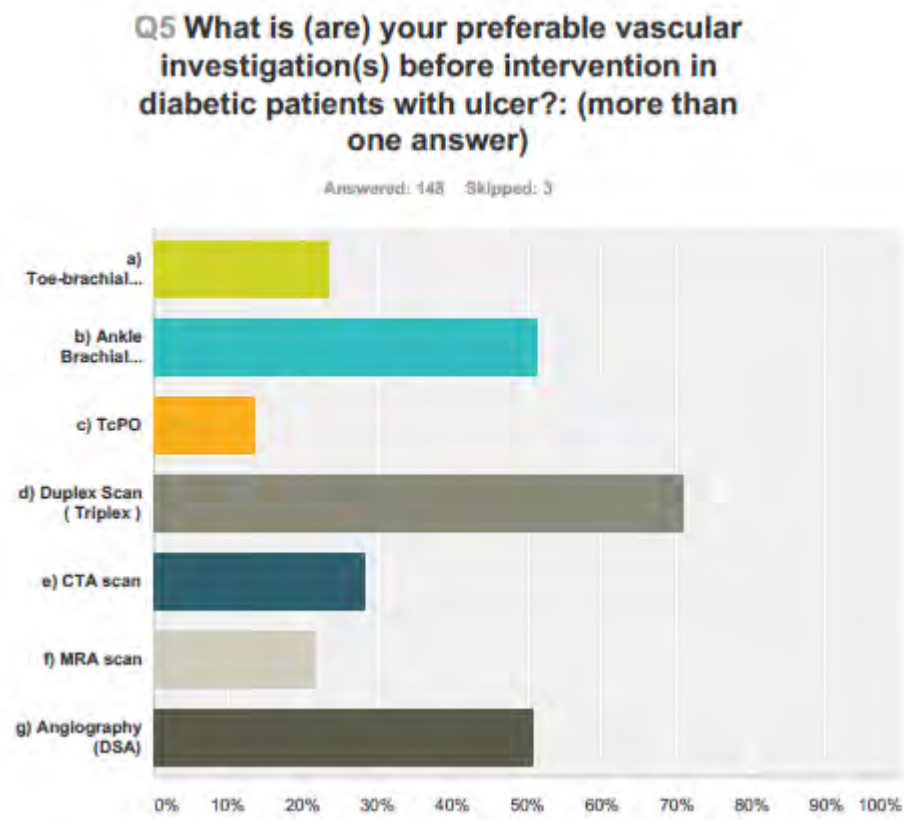
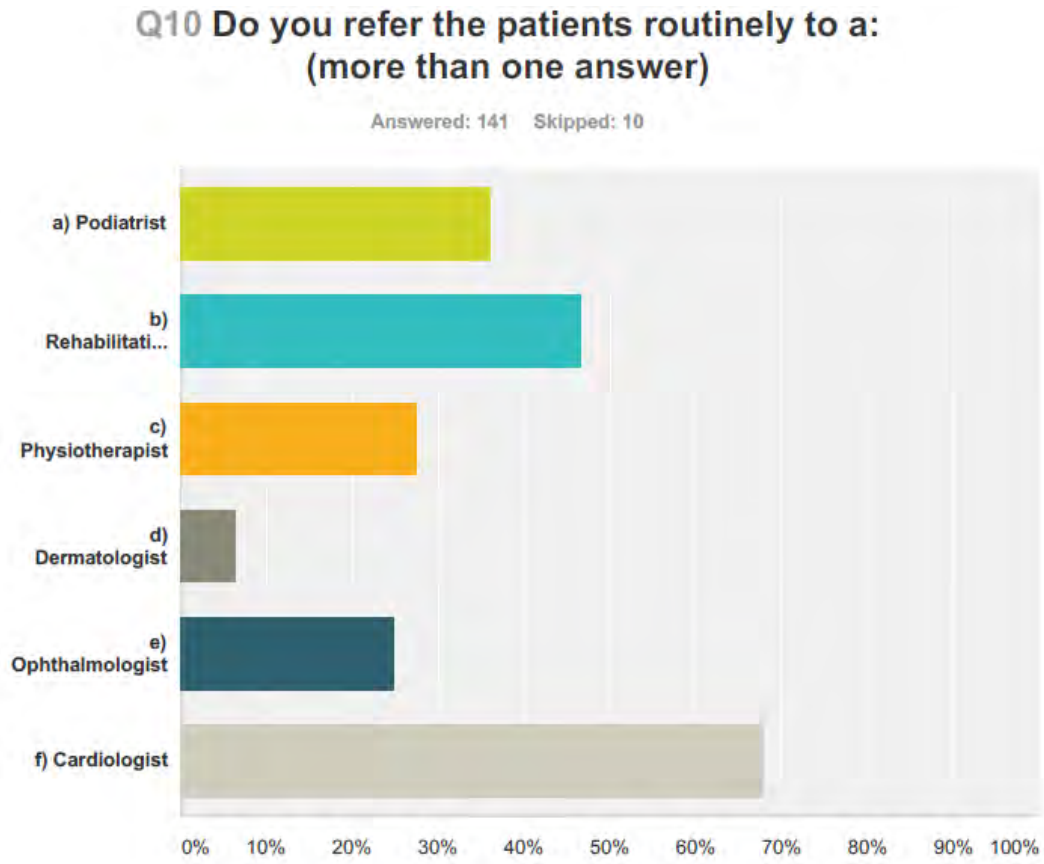


Figure 5. Question 10. (Rehabilitat: Rehabilitation physician)



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Validation of the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) questionnaire and its correlation with visual analogue pain scales in Greek population.

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Abstract

Introduction: One of the diagnostic tools of neuropathetic pain (NP) relies on screening questionnaires including the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) questionnaire.

Aim: To validate the LANSS questionnaire in Greek population. To assess any correlation between LANSS score and visual analog pain scales.

Methods: A prospective instrument validation study of LANSS was conducted in University Hospital of Larissa, on 70 patients (35 NP and 35 nociceptive pain), from April 2015-June 2015. Visual analog pain scales (VAS-ADL; impact of pain on daily living activities, VAS-INT; pain intensity) were also assessed and correlated with LANSS scale.

Results: The mean age of NP and nociceptive pain group was 67.11 ± 10.05 and 39.14 ± 17.07 years respectively. The mean LANSS score was $12.84 (\pm 9.27)$ in initial test, and $12.54 (\pm 9.41)$ in the retest evaluation. Cronbach's alpha was 0.895 and 0.901 at initial and retest examinations respectively, both values indicating good internal consistency. NP group had significant higher LANSS score than nociceptive pain group ($21.34 [\pm 1.39]$ vs $4.34 [\pm 4.86]$, $p < 0.01$). The sensitivity of LANSS questionnaire to distinguish neuropathic and

nociceptive pain was 94.29% (95% CI: 80.81-99.13%), while its specificity was 88.57 % (95% CI: 73.24-96.73 %).

A significant correlation was noticed between total LANSS score and VAS-ADL (initial r : 0.248; $p < 0.05$ and retest evaluation r : 0.288; $p < 0.05$).

Conclusion: The LANSS score is a reliable and valuable instrument to assess neuropathic pain in diabetic patients and to differentiate it from nociceptive pain in Greek population. In diabetic patients LANSS score is associated with impact on daily activities and potentially with quality of life.

Key words: diabetic neuropathic pain, nociceptive pain, LANSS score, validation.

Introduction

Peripheral neuropathy is characterized by diffused damage to the peripheral nerve fibres. The commonest cause of peripheral neuropathy is diabetes, and 30–90% of those patients with diabetes develop peripheral neuropathy.¹ Neuropathic pain (NP) is a well-known complication involving one-third of all diabetic patients.¹ It has a huge effect on a daily quality of life, both physically and mentally.² Thus, the symptoms of NP can be debilitating and cause sleep disturbances, anxiety and interfere with physical functioning.³ For this purpose, simple assisting instruments have been developed such as 10 cm visual analog scale which can easily and fast assess the impact of pain on activities of daily living (VAS-ADL) (0-10) and the pain intensity (VAS-INT) (0, no pain; 10, unbearable pain).^{4,5}

The diagnosis of NP relies on the clinical presentation and the existence of co morbidities of the patient and on screening questionnaires.^{6,7} Generally there are many types of categorization of pain, and one notably useful categorization has been the division in nociceptive pain versus NP. Nociceptive pain is provoked after neural pathways' activity caused by physical damage of the tissue or potentially traumatic-tissue related stimuli.⁸ Although the differential diagnosis of

NP is not formidable, it requires time and the acquisition of special diagnostic skills. To simplify this task, there are a number of diagnostic instruments, including the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) questionnaire which emerges for its suitability.⁹ The LANSS questionnaire has been already validated in Turkish,¹⁰ Brazilian,⁵ Chinese,¹¹ Portuguese,¹² and Greek.¹³ The use of validated translations of questionnaires helps to compare populations of different countries and cultures, which helps to establish protocols for global health. The aim of the present study was to apply the Greek version of the LANSS questionnaire on patients with diagnosed NP, to assess its validity and investigate any association of LANNS with visual analog pain scales (VAS-ADL and VAS-INT).

Material and Methods

Study design and data collection

We have conducted a prospective study in the University Hospital of Larisa, from April 2015 to June 2015. The inclusion criteria were: 1. Patients suffering from pain for 1 or more days (persistent and/or recurrent pain) 2. Education level: high school degree or above, be able to

understand Greek 3. Patients should have one of the following neuropathic or nociceptive pain diseases: Neuropathic pain: Diabetic patients with peripheral neuropathy. Nociceptive pain: Orthopedic non-diabetic patients with bruises, sprains, bone fractures, arthritic disorders and myofascial pain due to abnormal muscle stress.

Patients were enrolled only after confirmation by 2 pain clinicians with consistent diagnosis. The exclusion criteria were: 1. Patient without disposing capacity in their past medical history (such as schizophrenia, Alzheimer disease, et al) 2. Unable to read and write Greek 3. Patients with mixed pain.

The LANSS scale is comprised by a total of seven items including five questions regarding presentation of pain and two diagnostic items involving sensory tests for the presence of allodynia and decreased sensation to pinprick.⁹ A 23-gauge needle was used for pinprick test in contact with the patient's skin. If a pinprick was not felt in the area, the syringe was mounted onto the needle to increase the weight on the patient's skin. Hyperalgesia was considered to be present in cases in which the pinprick test was leading to an exaggerated painful response on the symptomatic area being compared with the normal one. Allodynia was also considered to be present when pain or unpleasant sensation was

provoked by lightly stroking cotton wool across the painful area and when normal sensation was experienced in the nonpainful site.

Patients' replies to the questions were a "yes or no" type and were evaluated differently depending upon the question. For this purpose we used the Greek validated LANNS questionnaire.¹³

Additionally, patients were asked to answer a 10 cm visual analog scale for the impact of pain on daily living activities of (VAS-ADL) (0-10) and a 10 cm visual analog scale for the pain intensity (VAS-INT) (0, no pain; 10, unbearable pain) at their first visit to the outpatient clinic. VAS-ADL represents a glimpse of quality of life of the patients while VAS-INT the overall perception of the patient for the intensity of pain.⁵ A LANSS score ≥ 12 was classified as neuropathic pain, and a score < 12 was classified as nociceptive pain.⁹ Retesting of the patients was performed within 2 weeks after initial evaluation.

Since there is no widely established a theoretical basis for determining sample size or power calculation in questionnaires psychometric validation,¹⁴ we have used the general rule of thumb for our sample size calculation. According to this rule, the minimum recommended participants size is between 5 and 10 times the number of questionnaire items.¹⁴ In our study we have considered the 5 to 1 ratio of participants to items for the sample size calculation of every group, thus

we recruited 35 consecutive patients with neuropathic pain from diabetic foot clinic and vascular surgery department and 35 consecutive patients with nociceptive pain from orthopedic department.

The study was approved by the University Hospital of Larissa review board. An approval has been obtained from the copyright holder for the use of LANNS questionnaire.

Data analysis

Internal consistency of the Greek LANNS questionnaire was evaluated by applying Cronbach's alpha test with a minimum acceptable value of 0.7.¹⁵ Test-retest reliability was evaluated by analysing the correlation between LANNS scores (total and score of each item) of the first visit at the outpatient clinic (test), and the retesting of the patients by using the Pearson's correlation coefficient. Furthermore, Bland-Altman plot was used to assess agreement between test and retest evaluations.

The validity of the questionnaire was demonstrated by examining the correlation between LANNS scores and the type of pain (Spearman's correlation coefficient), by comparing total scores between neuropathic and nociceptive pain groups with the Mann-Whitney U test, and by

assessing the sensitivity and specificity of LANNS for detecting neuropathic and nociceptive pain.

Furthermore, correlations between LANNS scores and the VAS-ADL as well as the VAS-INT were explored (Spearman's correlation coefficient), and the VAS-ADL and VAS-INT scores between neuropathic and nociceptive pain groups were compared with the Mann–Whitney U test.

Data analysis was performed using the SPSS 20 statistical software (IBM, Chicago, IL, USA). P values lower than 0.05 were considered as statistically significant.

Results

Neuropathic pain group consisted of 35 patients (28.6% female) with a mean age of 67.11 ± 10.05 (range 49 – 85) years. Nociceptive pain group consisted of 35 patients (37.1% female) with a mean age of 39.14 ± 17.07 (range 18 – 77) years.

LANSS questionnaire, VAS-ADL and VAS-INT were fully completed by all patients in their initial visit as well as in their retesting evaluation.

The mean LANSS score was 12.84 (\pm 9.27) in the initial test, and 12.54 (\pm 9.41) in the retest evaluation. Cronbach's alpha was 0.895 and 0.901 at initial and retest examinations respectively, both values indicating good internal consistency. All correlations between test and retest evaluation were significant ($P < 0.01$ level) for the total score and all LANSS items (Table 1). Bland-Altman Plot (Figure 1) showed that the 95% limits of agreement ranged from -2.768 to 2.968 , while almost all differences were located between the agreement thresholds.”

LANSS score was strongly correlated with the type of pain in both test ($r: 0.896$; $p < 0.01$) and retest ($r: 0.893$; $p < 0.01$) evaluations. The mean LANSS scores of the neuropathic and nociceptive pain groups were 21.34 (\pm 1.39) and 4.34 (\pm 4.86) in the first evaluation and 21.34 (\pm 1.34) and 3.74 (\pm 4.30) in the retesting respectively. Neuropathic pain group had significant higher LANSS scores ($p < 0.01$). The sensitivity of LANSS to distinguish neuropathic and nociceptive pain was 94.29% (95% CI: 80.81-99.13%), while its specificity was 88.57 % (95% CI: 73.24-96.73 %).

A significant correlation was noticed between total LANSS score and VAS-ADL in both initial ($r: 0.248$; $p < 0.05$) and retest evaluation ($r: 0.288$; $p < 0.05$); while there was no significant correlation between total

LANSS score and VAS-INT in both initial ($r: 0.044$; $p = 0.716$) and retest evaluation ($r: 0.029$; $p < 0.814$). VAS-ADL was significantly higher in neuropathic pain group ($p < 0.05$), while no significant difference was noticed in VAS-INT between the two groups.

Discussion

The neuropathic pain differs from nociceptive pain both in etiology and clinical presentation.^{1,2,8} The early diagnosis and treatment is crucial for better prognosis especially in diabetic patients, who develop complications such as diabetic foot.¹⁶ However, current existing examinations, such as nerve conduction velocity and somatosensory evoked potential, do not have high specificity.¹¹ Quantitative sensory testing with high specificity requires expensive equipment,¹⁷ while skin biopsy is not easily accepted by patients due to its traumatic feature. Physicians should be able to use tests and examinations with high sensitivity and specificity to diagnose neuropathic pain with a minimum cost. Therefore, many neuropathic pain questionnaires have been developed in recent years.

NP questionnaires are efficient diagnostic tools for differential diagnosis of neuropathic pain^{5,6,7,9,10,12,13} Even those physicians who have

a little experience about neuropathic pain, they can easily use them in their practice to diagnose NP.⁷ Additionally, most NP questionnaires have high sensitivity and specificity, they do not require special equipment or examinations, and they maintain the cost low. Thus, NP questionnaires are highly efficient and cost effective.⁶

Until recently in Greece, no questionnaire for NP had been validated. The Douleur Neuropathique 4 (DN4) was the first questionnaire that was validated in Greek, for diagnosis of NP and showed good potential as discriminatory tool of neuropathetic element of pain.¹⁸ Besides, during last years in Greece, physicians' efforts have been escalating to translate in Greek and validate various questionnaires concerning other specialties^{19,20,21} aiming to play an important role in epidemiological studies and to establish the incidence of various pathologies.

The internal consistency of the Greek translation of LANSS¹³ was analyzed in our study. Internal consistency measures how efficiently the scores for the individual items of the instrument correlate with each other.²² The minimum acceptable value for Cronbach's alpha test to represent and evaluate internal consistency is 0.7.¹⁵ In our study, Cronbach's alpha was 0.895 and 0.901 at initial and retest examination respectively, both values suggesting very good internal consistency of the

Greek LANSS. Those rates were according to the line or even higher than previous reports^{5,10,11,12} (Cronbach's alpha values 0.67-0.824) even when being compared with the study which translated, adapted and validated the Greek LANSS questionnaire at first place.¹³

Test-retest reliability shows stability of calculated scores with repeated testing and can be assessed by correlating initial test and subsequent retest scores.²² In our study, correlations of test-retest evaluation were statistically significant for total LANSS score as well as for questionnaires' items. Similar correlations have been reported from other countries.^{11,12}

Validity is the degree to which an instrument measures what it is supposed to measure.²³ In other words, it is the ability of an instrument to distinguish between patient groups who have or do not have the disease being studied. In our study, validity of the Greek version of the questionnaire was assessed by examining the correlation between LANNS scores and the type of pain, by comparing total scores between neuropathic and nociceptive pain groups, and by assessing the sensitivity and specificity of LANNS for detecting neuropathic and nociceptive pain. The Greek LANSS proved to be a valid instrument, since total score was strongly correlated with the type of pain; neuropathic pain group had significant higher LANSS scores; while the sensitivity and specificity of

were 94.29% and 88.57% respectively. This has been also been proven in the Batistaki et al.¹³ study, although the sensitivity rate was lower and specificity rate was higher (82.76% and 95.24% respectively). Those percentages are according to the line with previous reports that have shown similar or even lower rates of sensitivity and specificity between NP and LANNS score and have been used as important diagnostic tool in other countries.^{5,10,11,12}

In our study, it was shown that there was a significant correlation between LANNS score and VAS-ADL while there was no such relation noticed for VAS-INT. Thus patients with higher LANNS score (in our case diabetic patients), answered that their pain had a greater impact on daily living activities, although the severity of the pain (VAS-INT) did not differ from that of patients with nociceptive pain. Thus, NP may have a great impact on quality of life of diabetic patients and their daily activities, although this phenomenon is not always associated with the intensity of the pain. Schestatsky et al. (2011) have demonstrated similar results supporting the negative role of NP on daily activities in diabetic patients.⁵ In addition, there have been many reports previously which have showed that NP of diabetic foot impacts significantly the diabetic patients' quality of life.^{3,24,25}

Besides the value of LANNS score questionnaire is useful for every physician in the diagnosis of NP, it may play an important role in epidemiological studies, aiming to establish the incidence of neuropathic pain in various countries.²⁶

There are some limitations in our study. Even though there is no widely established theoretical basis for determining sample size or power calculation in questionnaires psychometric validation,¹⁴ our sample size is relative small compared to the other LANSS validation studies^{5,11,12}. We have also excluded patients with mixed pain so that our two study groups will be more homogenous and give more accurate results. This is also a limitation, since it could imply a bias of our study. One other potential limitation inherent in our study is the difference in the mean age between patients with NP and nociceptive pain. Nevertheless, it has not been reported any significant association among patients with NP or nociceptive pain and age.^{1,2,3,6,8} Finally, although we did not assess the impact of NP on quality of life with validated questionnaires, VASs have provided us a short information about the influence of NP on diabetic patients' daily activity, which consists a rough approach of quality of life.

Conclusion

The LANSS score is a reliable and valuable instrument to assess neuropathic pain in diabetic patients and to differentiate it from nociceptive pain in Greek population. In diabetic patients LANSS score is associated with impact on daily activities and potentially with quality of life.

Conflict of interest:

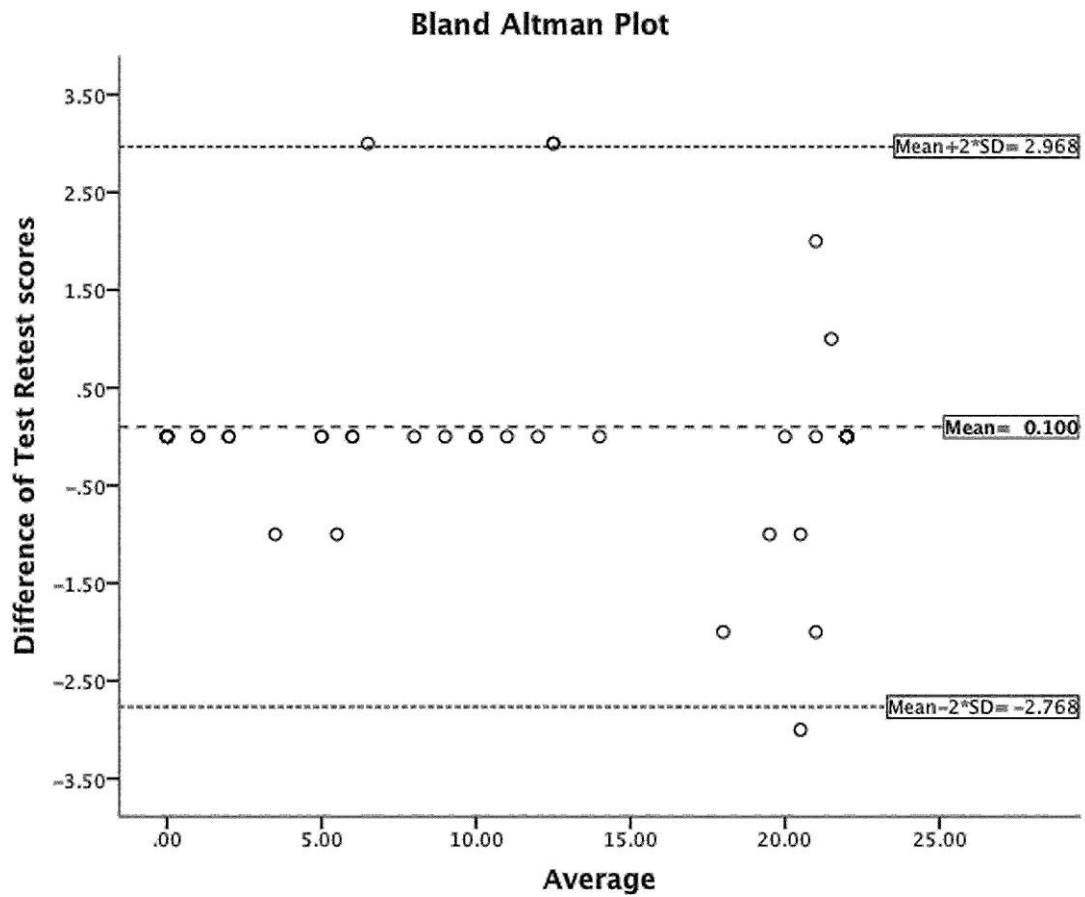
None of the authors had any conflict of interest.

Table 1. Test-retest reliability for LANSS questionnaires.

	Test-Retest Reliability
	Pearson's correlation coefficients between scores of test and retest LANSS questionnaires
LANSS total score	0.937**
1 st Question of LANSS	0.970*
2 nd Question of LANSS	0.913*
3 rd Question of LANSS	0.913*
4 th Question of LANSS	0.971*
5 th Question of LANSS	0.912*
6 th Question of LANSS	0.990*
7 th Question of LANSS	0.972*

* P<0.01

Figure 1: Bland-Altman Plot: The 95% limits of agreement ranges from -2.768 to 2.968 .



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Factors associated with ulcer healing and quality of life in patients with diabetic foot ulcer.

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Original Article

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Abstract:

A prospective non-randomized cohort study on consecutive diabetic patients with foot ulcer was undertaken, to assess factors associated with the healing process or limb salvage, and evaluated the impact of their treatment on their quality of life (QOL). QOL was evaluated using diabetic foot ulcer scale-short form questionnaire (DFS-SF) before and after treatment. A total of 103 diabetic patients with ulcer (mean age 69.7 ± 9.6 years, 77% male) were treated and followed up for 12 months. Ulcer healing, minor amputation and major amputation rates were 41, 41 and 18%, respectively while mortality rate was 18%. Ulcer healing was associated with University of Texas wound grade I and the SIDESTEP trial's diabetic foot infection wound score. Limb loss was associated with non-palpable popliteal artery, longer in-hospital stay and delay until referral. QOL was improved in all domains of DFS-SF ($p < 0.0001$) throughout the cohort of our patients regardless of their outcome and no outcome (healing, minor or major amputation) was superior to other. Significant improvement was observed in all domains of hygiene self-management after consultation during follow up period.

Key words: Diabetic foot; ulcer; quality of life; limb loss.

Introduction

The International Diabetes Federation (IDF) reported that the global prevalence of diabetes (DM) in adults was 8.3% in 2013 expecting to rise beyond 592 million by 2035 with a 10.1% global prevalence.¹ One of the most insidious complications of DM is foot ulcer (DFU) and according to the World Health Organization (WHO), all foot complications may be encompassed under the term diabetic foot syndrome defined as “ulceration of the foot associated with neuropathy and different grades of ischemia and infection.”² DFU was always a multinational burden and in recognition of this reality the St. Vincent Declaration in 1989 included a set of goals for the health care of people with DM.³ In response to the emerging pandemic of DM type 2, after this declaration, several other regional partnerships between the IDF and WHO, proceeded with their own declarations such as: the Declaration of the Americas or DOTA (1996),⁴ the Western Pacific Declaration on Diabetes (WPDD 2000)⁵ and the Declaration and Diabetes Strategy for Sub-Saharan Africa (2006).⁶

Various wound classification systems have been developed, so there will be a common ‘language’ among the physicians and a helpful tool in the planning and monitoring of treatment and in predicting the outcome of ulcer healing and assessing the associated factors.^{7,8,9,10,11}

Many practical guidelines have been published with most recent one the evidence-based global consensus for the prevention and management of diabetic foot by the International Working Group on the Diabetic Foot (IWGDF) Editorial Board.¹²

Along with increased morbidity, foot ulcers can lead to lifelong disability and may substantially diminish the quality of life (QOL) for these patients.¹³ Specifically, patients with DFU have restrictions on mobility, poor psychosocial adjustment, and lower self-perceptions of health than patients who do not have ulcers.^{13,14} An understanding of the specific effects of DFU on individual patients' QOL is central to the direction of treatment, adherence to treatment, and patient/practitioner communication.

The aim of this observational study was primarily to assess the factors associated with the healing process or limb salvage in diabetic patients with foot ulceration. We also evaluated the impact of treatment and QOL outcomes.

Methods

A prospective non-randomized cohort study on consecutive diabetic patients with foot ulceration was undertaken in a Mediterranean country (Central Greece, an area with mainly agricultural production) by

a tertiary centre which has the only existing foot clinic service in the region. These were patients with DM type 2 suffering from lower limb ulceration who were referred to our service either at the outpatient clinic or as an emergency. Exclusion criteria were: i) malnutrition (body mass index: BMI < 18), ii) immobility (bed or wheel chair bound or stroke limb), iii) immune-suppression, and, iv) lacking mental capacity to consent to the study.

The patients were under close follow up since their first assessment and had regular appointments in the outpatient clinic of our service depending on their ulcer healing progress. On the first visit, demographics (age, sex, height, weight, body mass index-BMI) and personal details (residence address, occupation, carer identity) and the past medical history, including duration of DM, history of hypertension (HT), hyperlipidemia (HL), coronary artery disease (CAD), atrial fibrillation (AF), peripheral artery disease (PAD), chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), cerebrovascular disease (CVD), ophthalmopathy, history of smoking and alcohol, antiplatelet and statin therapy were recorded. Additionally, family history of HT, HL and DM was also recorded.

In addition, all patients received clinical assessment by a Vascular Surgeon, including palpation of the peripheral arteries, Ankle brachial

index (ABI) measurement, ulcer evaluation and a recording of self-management hygiene (self-examination, foot washing, foot hydration, the way of cutting their nails, walking barefoot and usage of special anatomical shoes). Ulcer evaluation was undertaken according to three grading systems: i) the University of Texas wound classification which is a system for diabetic foot wounds that evaluates wound depth, the presence of infection, and peripheral arterial occlusive disease in every category of the wound assessment,⁹ ii) the diabetic foot infection (DFI) wound score based on SIDESTEP trial (Study of Infections in Diabetic feet comparing Efficacy, Safety and Tolerability of Ertapenem versus Piperacillin/tazobactam) with the measurement of 10-items,¹⁰ and, iii) the Society for Vascular Surgery developed a Lower Extremity Threatened Limb Classification System in which the risk stratification is based on 3 major factors that impact amputation risk and clinical management such as wound, ischemia and foot infection (WIFI).¹¹ The goal of all these systems is to improve communication, leading to a less complex, more predictable treatment course and, ultimately, an improved result.

Additionally, neuropathic pain (NP) was also assessed using LANSS (Leeds Assessment of Neuropathic Symptoms and Signs) scale questionnaire.¹⁵ Patient replies to the questions were a “yes or no” type

and were evaluated differently depending upon the question. For this purpose we used the Greek validated LANSS questionnaire.¹⁶

Since this is an observational study, each Vascular Surgeon could decide on the diagnostic investigations needed [foot X-Ray, Duplex scan, Computed Tomography Angiography (CTA), Digital Subtraction Angiography (DSA)] and on the type of treatment (open surgery, endovascular, hybrid procedures or conservative). Primary outcomes were ulcer healing and minor or major amputation. Analysis of the factors associated with the primary outcomes was undertaken. Secondary outcomes were the impact in QOL after each type of treatment and self-management at 12-month follow up.

A multidisciplinary approach program was established in our hospital regarding these patients.

Regarding the assessment of patient QOL, we used the Greek version of Diabetic Foot Ulcer scale- short form (DFS-SF) as translated by Mapi Research Trust-All (Copyright © 2015 rights reserved).¹⁷ The DFS was developed to measure the impact of diabetic foot ulcers on QOL issues most important to patients. The DFS was also translated into several languages using both forward and backward translations and cognitive debriefing to ensure cultural equivalence. The DFS contains a total of 64 items, 58 of which are used to compute 15 QOL subscales.¹⁸

The 6 remaining items address employment-related issues and are not included in computation of subscale scores on the DFS long form.

The final version of the DFS-SF (short-form)¹⁷ which is used broadly contains a total of 29 items grouped into six subscales:

- Leisure (5 items)
- Physical health (5 items)
- Dependence/daily life (5 items)
- Negative emotions and worried about ulcers/feet (10 items)
- Bothered by ulcer care (4 items)

Thus, each patient had to fill the DFS-SF questionnaire during the first examination, and after 12 months of follow up. Also, the QOL was analyzed in respect to the ulcer treatment, the patient's residence and the level of their home care. Additionally, Visual Analogue Scales for the impact of pain on daily living activities of (VAS-ADL) (0–10) and a 10 cm visual analog scale for the pain intensity (VAS-INT) (0, no pain; 10, unbearable pain)¹⁵ were recorded at their first visit to the outpatient clinic and their last one.

This study involved the collection of existing data and diagnostic tests that have been recorded in such a manner that subjects could not be identified, either directly or through identifiers linked to the subject.

However, the protocol and informed consent were approved by the Institutional Review Board.

Statistical analysis

The relationships of categorical variables and the main outcomes observed (ulcer healing, minor amputation, major amputation, mortality) was examined with the use of the Chi Square statistic, while the relationships between main outcomes and continuous measurements was assessed with the independent samples t-test or the Mann Whitney test, where appropriate. The findings were assessed and the statistically significant variables were entered in a binary logistic regression model. The two way interaction effects were also considered to reach the final model for each outcome. For the change in the Quality of life Measures the Paired samples t-test was applied for each of the dimensions measured. Statistical significance was set at 0.05 (two-sided). The analysis was carried out with the use of SPSS v.21.0

Results

Over a period of 2 years (2012-2014) 103 consecutive patients with diabetic foot ulcer entered into the study and were followed up for 12 months. Only 2 patients were already excluded due to the exclusion

criteria. The mean age of the patients was 69.7 ± 9.6 years and most of them were males (76.7%, 79/103). More than half of the patients were manual workers and almost everyone was cared for by family members. The population was overweight with mean BMI of 28. Most of the patients were on antiplatelet (80%) and statin (70%) therapy, while half of them were also on insulin. Social-demographics, past-medical history details and blood test results are presented in table 1.

Almost half of the patients (47%, 49/103) presented directly to our hospital as an emergency, while 20% (21/103) were referred by an endocrinologist, 11.5% (11/103) by a general surgeon, 11.5% by a general practitioner (GP), 3.8% (4/103) by another vascular surgeon, 3% (3/103) by an internal medicine physician, 2% (2/103) by a nephrologist, 1% (1/103) by a neurologist and 1% (1/103) by an orthopedic department. The mean time until referral to our service was 23.8 ± 9 days. There was no difference between patients with self-referral and physician referral. However, there was a seasonal variation in the presentation and referral of these patients to our service peaking in colder months during the year (autumn and winter, 64%, 66/103 vs spring and summer 36%, 37/103, $p < 0.05$). The most common cause of ulcer was trauma (lack of attention 68%, 70/103; shoe wearing trauma 11.7% ,12/103); after great saphenous harvesting 2% (2/103); after nail cutting 1% (1/103); and 17.5% (18/103)

by unknown cause. The ulcers were confined mainly to toes (64%, 66/103), and less frequently to the shin (9.7%, 10/103), the sole (7.8%, 8/103), the heel (7.8%, 8/103), the dorsal surface of the foot (5.8%, 6/103), the ankle (2.9%, 3/103) and in a previous amputation stump area (1.9%, 2/103) (Figure 1).

In table 2 patients are categorized according to the University of Texas wound classification system (i) and according to the Lower Extremity Threatened Limb Classification System (WIFI) (ii). Additionally, the mean DFI wound score was 20.4 ± 3 , while the mean LANSS score was 20.5 ± 3.4 (all patients in our study had LANSS score > 12).

During 12 month of follow up, 41% (42/103) of the patients had their ulcer healed. From this group, 40.5% (17/42) of the patients were healed in the first month, 85.7% (36/42) in first 3 months and 97.6% (41/42) in first 6 months. A further 50.5% (52/103) of the patients underwent a minor amputation, 63% (33/52) of which during first hospitalization, 88.5% (46/52) during first 3 months and 98% (51/52) during first 6 months after initial presentation. All but 9 patients achieved healing of their minor foot amputation. These 9 patients along with another 9 underwent major amputation accounting for a 17.6% (18/103)

limb loss. Most of the amputations (14/18, 77%) were undertaken in first 6 months.

After multiple logistic regression analysis including characteristics of tables, referral characteristics and ulcer location and causes, ulcer healing was associated with University of Texas wound classification and DFI wound score. Patients with TEXAS grade I ulcer had 23-fold more often ulcer healed (95% CI 2.3-220, $p=0.007$) than those with a higher grade. Additionally, after increase of one DFI score unit, the odds risk for ulcer non-healing is increased by 15% (95% CI 1.5-30%, $p=0.028$), with mean DFI score 17 ± 2 for ulcer healed patients and 24.5 ± 3 for non-healed patients. (Figure 2)

Minor amputation was associated with Texas classification, COPD and LANSS score. Patients with TEXAS grade II or higher had 11.3 increased odds risk for minor amputation (95% CI 3.4-38, $p<0.001$) than those with grade I. Additionally, patients with COPD had 12.3 increased odds risk for minor amputation (95% CI 2.1-73 $p=0.006$), while for every increase of one unit of LANSS score the odds risk for minor amputation is increased by 43% (95% CI 2-100%, $p=0.040$). (Figure 3)

Major amputation was associated with palpable pulses of popliteal artery, hospital stay and time until referral. Every patient with non-palpable popliteal artery had 5.2 increased odds risk for major amputation

(95% CI 1.03-26 p=0.045). For each additional hospital stay the odds risk for a major amputation increased by 8% (95% CI 2-14% p=0.007).

Finally, for each additional day of delay until referral the odds risk for major amputation increased by 3.5% (95% CI 1-6% p=0.011).

Among patients with evidence of ischemia requiring revascularization, no differences were observed in respect to healing rate, minor and major amputation according to the type of intervention; 36 patients underwent 38 procedures: 20 endovascular only, 9 open only and 9 hybrid ones and the total healing rate was 30.5% (11/36). In patients who were not considered candidates for revascularization (67/103), a reasonable healing rate was observed (46%, 31/67).

Lack of multidisciplinary assessment was observed in a large number of patients and therefore during their initial hospitalization they were referred for evaluation to other services: 65 (63%) patients to Endocrinology for DM control, 34 (33%) to Cardiology, 8 (7.7%) to Nephrology, 8 (7.7%) to Ophthalmology, 6 (5.8) to Orthopedics, 4 (3.8) to a Chest Medicine and 1 (1%) to Neurology.

The mortality rate was 17.5% (18/103) during the 12 month period. Myocardial infraction (MI) accounted for the majority of deaths (72%, 13/18), while 3 patients died because of severe sepsis and 1 due to acute renal failure. After multivariate analysis only age was associated with

death. For each one additional year of age, the risk of death was increased by 17% (95% CI 7 -29% $p=0.001$). During 12-month follow up no patient had a development of a new ulcer or a deterioration of a healed one.

All alive in 12 month-follow up patients completed the QOL questionnaire (DFS-SF) in their first and the last assessment (12-month follow up); 82.5% (85/103) were available for QOL assessment at 12-month follow up. QOL was significantly improved in all domains of DFS-SF ($p<0.0001$) throughout the cohort of our patients after their treatment as compared with their condition before treatment. (Table 3) In addition, after further analysis, it appeared that the improvement of QOL was not associated with the type of treatment and the outcome, thus there was no difference in improvement of QOL among patients regardless of whether they had their ulcer healed or had undergone an amputation. The lower improvement in QOL was demonstrated in domains related to physical health (mean increase 9.9), dependency in daily life (mean increase 10.9), treatment satisfaction (mean increase 12.4) and higher improvement in domains related to leisure (mean increase 16.5) and negative emotions (mean increase 18.2). Finally, when QOL was analyzed according to the patient residency area and the caring person, no correlation was identified. A significant improvement was observed in all

domains of hygiene self-management between the first and the last assessment (12 months) of follow up while VAS of both types were improved significantly during follow up.(Table 4)

Discussion

In our study, the mean duration of DM among patients was 18 ± 3 years. However, it was demonstrated that their actual awareness about the nature of the disease was inadequate. Thus, 50% of our patients presented to our service late from the onset of the ulcer (mean time 24 days), with a poorly controlled DM (mean Hb1AC: 8.1% and BMI: 28) and low awareness of hygiene self-management (table 3). It has been previously demonstrated that foot self-care is generally infrequent, and clinical monitoring in outpatient clinics is performed for less than half of diabetic patients with foot ulcers.¹⁹ In practice, patient education aiming to promote foot care knowledge and self-examination is advocated by most experts and guidelines as an important strategy to prevent diabetic foot complications. Education of patients at high risk of or with ulceration is considered to be particularly important.²⁰ In some trials, foot care knowledge and self reported patient behavior seem to be positively influenced by education in the short term.²¹ In our study after many

consultations of our patients during follow up, they managed to improve their hygiene self-management status considerably (Table 4), decreasing the likelihood of a new ulcer. However, the effect of patient education is still in doubt and there is insufficient robust evidence that limited patient education alone is effective in achieving clinically relevant reductions in ulcer and amputation incidence.²¹ Additionally, in our study, almost half of the patients had a late referral by their physician, and thus it would seem advisable to implement strategies oriented towards the improvement of primary care physician awareness of diabetic foot and its complications, along the IWGDF recommendations that healthcare professionals should receive periodic education to improve the care of high-risk individuals.¹² It is true that such patients may neglect themselves because of various reasons including impaired sensation due to neuropathy, impaired vision as a result of retinopathy, and other co-morbidities including cardiac and renal impairment which all may contribute also to the lack of a personal alarm system.^{22,23}

It is still debatable whether ulcer healing in diabetic patient always requires revascularization. Although, in a recent systematic review, it was demonstrated that improved rates of limb salvage were associated with revascularization compared with the outcomes of conservatively only treated patients, there were insufficient data to recommend one

method of revascularization over another.²⁴ Along this line, in our study, no differences were observed in respect to healing rate, minor and major amputation according to the type of intervention. However, this was an observational study and not designed to compare those treatments. Over the last decade, there has been a marked shift from open revascularization to an endovascular one in diabetic patients with foot ulcer²⁵ and in some centers endovascular treatment is used first as "preliminary approach" for critical limb ischemia and diabetic foot.²⁶ Additionally, in patients who were not considered candidates for revascularization, a reasonable healing rate was observed (46%, 31/67). Recently, it was suggested that even diabetic patients with ischemic foot ulcers not available for revascularization, should not be excluded from healing without major amputation.²⁷

The SIDESTEP trial has demonstrated that the clinical response was less favorable at the follow-up assessment in patients with a DIF score >19.¹⁰ Along this line, our study showed that patients with healed ulcer had a score of mean value 16.8 (figure 2). Another important factor that was associated with ulcer healing was the TEXAS classification during first examination. Thus, it seems that initial clinical evaluation with the use of DFI score and TEXAS classification may help physicians to identify which patients are at increased risk for non-healing ulcers or

even limb loss, and in whom closer follow up and more aggressive treatment may be indicated.

As far as the predictive factors associated with limb loss are concerned, it has been previously demonstrated that male gender and the presence of neuropathy,²⁸ Severity of Diabetic Foot Infection,²⁹ elevated fasting blood sugar,³⁰ WBC and PAD,³¹ are associated with amputations. In our study, Texas classification, COPD and LANSS score were associated with minor and delay of hospital referral, the severity of PAD, and the prolonged hospitalization were associated with major amputation. It seems that detailed initial clinical assessment and fast-track management of DFU are important factors associated with limb loss. Furthermore, it is of note that the majority of deaths in our cohort were cardiac related. This underlines the importance of cardiovascular disease risk factor control as primary prevention in patients with DM 2 as it has been recommended from the American Heart Association and the American Diabetes Association.³²

The evaluation of the patient QOL has been recognized as an important area of scientific knowledge, since the concept of QOL has been related to the notion of health: satisfaction and well-being in the physical, psychological, socio-economic and cultural spheres.³³ According to the WHO, QOL can be defined as an individuals'

perception of their position in life in the context of the culture and value systems in which they live in and in relation to their goals, expectations, standards and concerns.³⁴ Studies have evaluated and reported on QOL in diabetic patients with ulcer and compared them with other control groups.^{13,34-38} Presence or history of diabetic foot ulceration has been proved to have a large impact on physical functioning and mobility.³⁸ Diabetic foot ulcer patients had much worse health related QOL (HRQL) compared with the diabetes population and the general population, especially in physical health.^{13, 36-38} Our study is the first to our knowledge that evaluates the QOL in the same group of patients before and after treatment. Thus, in our study the presence of diabetic foot ulcer was associated with poor QOL, and QOL was significantly improved in all domains of throughout the cohort of our patients after the ulcer management. However, it was interesting, that QOL was improved regardless of patient outcome (healing, minor or major amputation) and no outcome was superior to another. Similarly, VASs were improved after treatment in our cohort. Even in cases that a major amputation was undertaken, the patients perceived their situation as improved in terms of QOL. A recent report was in agreement with that outcome, suggesting that clinicians should not assume that patients will experience poorer QOL outcome only because they underwent an amputation.³⁴ An

understanding of the specific effects of chronic diabetic foot ulcers on individual patient QOL is central to the direction of treatment, management of compliance, and patient/practitioner communication.

Patients with a diabetic foot ulcer should to be assessed holistically, thus intrinsic and extrinsic factors should be addressed and managed by a multidisciplinary diabetic foot team (MDFT) of physicians as soon as possible (within one working day of presentation or even immediately in the presence of severe infection).^{12,39,40} However, in many hospitals not only in our country, but also in the Mediterranean region,⁴¹ a MDFT approach has not been adopted and physicians have to work as individuals on diagnosis and management and attempt to refer patients to other specialties when they consider that it is necessary. Studies, have demonstrated that the introduction of a MDFT has been associated with a reduction in the incidence of major amputations in patients with DM.^{42,43}

Potential selection and treatment biases may exist as about 50% of patients had PAD, because this study was a prospective observational one, in patients referred to the Vascular Service of a tertiary Hospital. However, this reflects the real world practice of a Vascular Service which inevitably is committed to deal with more difficult-to-heal ulcers.

Conclusions

Our observational study showed that delayed hospital referral, prolonged hospitalization and absence of popliteal pulses were associated with limb loss. Additionally, initial clinical status assessment with DFI score and TEXAS classification may predict ulcer healing. QOL improved in all patients after treatment regardless of the outcome (healing or amputation). Also, improvement was observed in the hygiene self-management.

No conflict of interest.

None

Author contribution

All authors contributed to: (1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, and, (3) final approval of the version to be published.

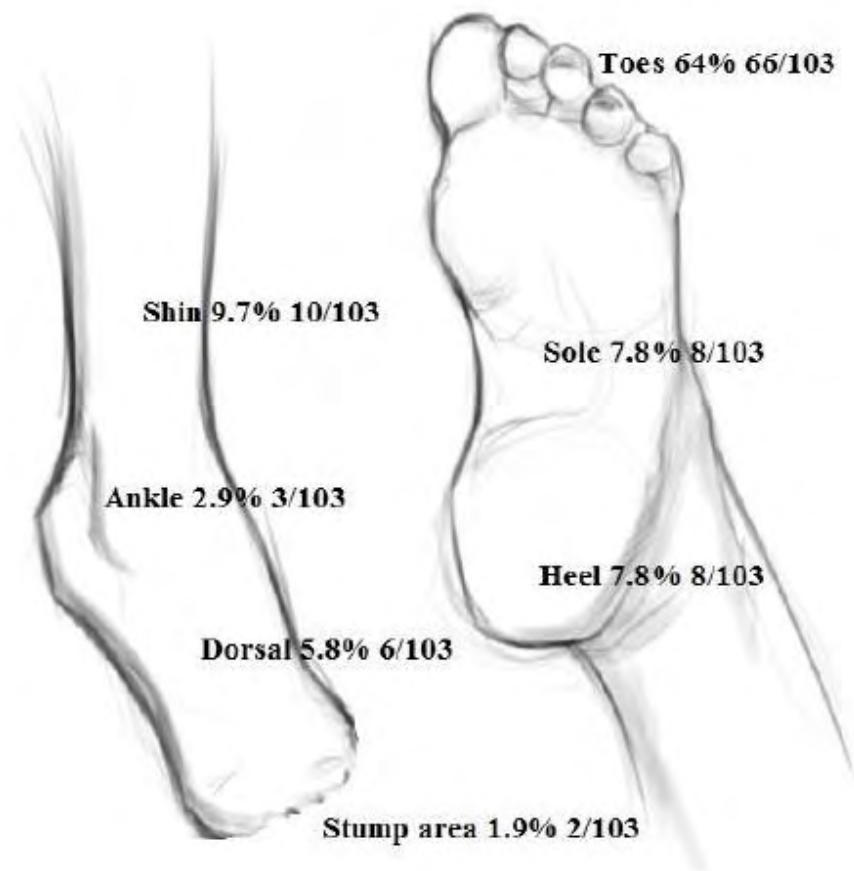


Figure 1. Schematic location of the ulcers.

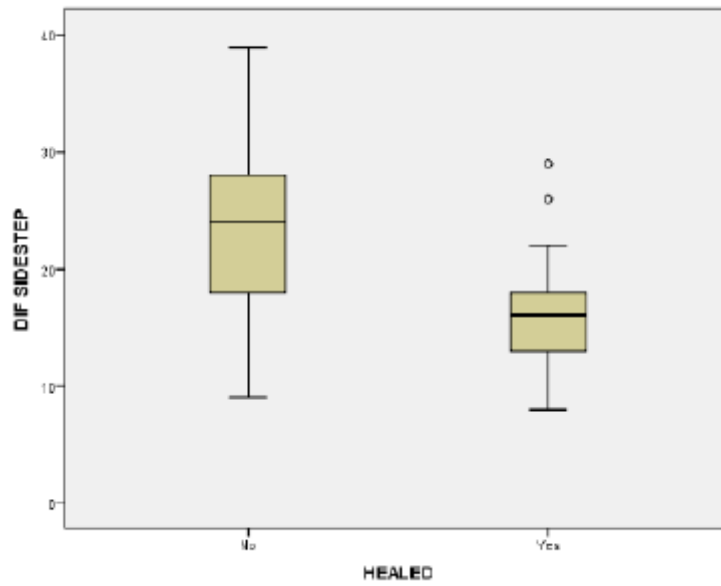


Figure 2. After increase of one DFI score unit, the risk for ulcer non-healing is increased by 15% (95% CI 1.5% - 30%, $p=0.028$), with mean DFI score 17 ± 2 for ulcer healed patients and 24.5 ± 3 for non-healed patients (DFI: diabetic foot infection; CI: confidence interval)

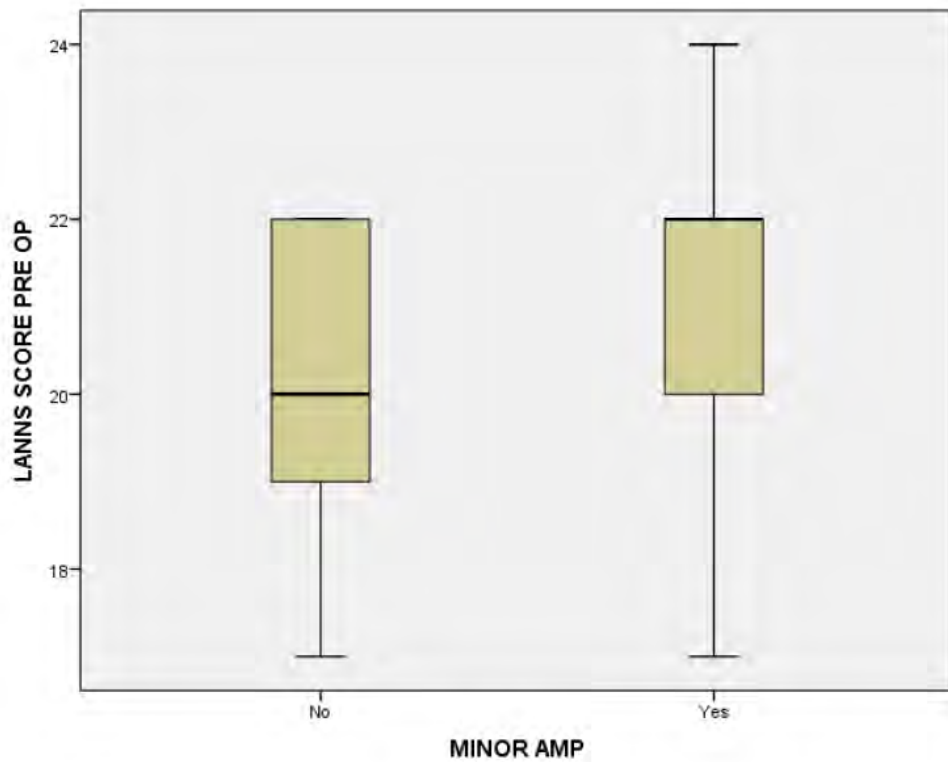


Figure 3. For every increase of one unit of LANSS score the risk for minor amputation is increased by 43% (95% CI 2% – 100%, $p=0,040$). (LANSS: Leeds Assessment of Neuropathic Symptoms and Signs, CI: confidence interval)

Socio-Demographics		Past medical history		Blood test	
Sex	76.7% Males (79/103)	Type of Diabetes	100% Type 2		Mean±SD
Age in years	69.7±9.63	Mean duration of DM in years	17.7±7.9	Hb	11.9±1.7g/dL
Mean height in cm	164.7±24.4	HT	93.2% (96/103)	WBC	13±3 10 ³ /μL
Mean weight in kg	79.23±16.7	CAD	55.3% (57/103)	Neu	72.8±9.5%
Mean BMI in kg/m²	28±5.1	AF	12.6% (13/103)	PLT	277±111 10 ³ /μL
Residency		PAD	53.4% (55/103)	MPV	8.6±1.2 fL
Urban	53.4% (55/103)	Mean ABI R	0.9±0.3	ESR	36.8±20.3mm/h
Countryside	46.6% (48/103)	Mean ABI L	0.7±0.2	CRP	4.9±2.4mg/dL
Occupation		Patients with non- compressible ABI	29% (30/103)	Cr	1.0±0.3mg/dL
White collar worker	25.2% (26/103)	DSA	38.8% (40/103)	Ur	45±26mg/dL
Manual worker	54.4% (56/103)	CTA	2% (2/103)	Na	137.2±14mmol/L
Unemployed	20.4% (21/103)	CRD	20.4% (21/103)	K	4.6±1.2mmol/L
Home carer		HL	74.8% (77/103)	ALT	24±24 IU/L
Spouse	46.6% (48/103)	COPD	11.7% (12/103)	AST	28±25 IU/L
Descendants	47.6% (49/103)	CVD	12.6% (13/103)	CK	106±97U/L
Alone	5.8% (6/103)	History of alcohol consumption	23.3% (24/103)	LDH	202±92IU/L
Family history of DM	44.6% (46/103)	History of smoking		Bilirubin	0.5±0.3mg/dL
Family history of PAD	15.5% (16/103)	No	27.2% (28/103)	Total Chol	167±52mg/dL
Family history of CAD	76.7% (79/103)	Yes	25.2% (26/103)	Trig	168±73mg/dL
		Ex smoker	47.6% (49/103)	LDL	111±49mg/dL
		History of ophthalmopathy		HDL	42±14mg/dL
		None	25.2% (26/103)	INR	1±0.3
		Mild	42.7% (44/103)	APTT	32.3±6sec
		Moderate	22.3% (23/103)	PT	18.2±5sec
		Severe	9.7% (10/103)	HbA1C	8.1±1.2%
				Negative ulcer cultures	17063% (65/103)

Table 1. Social-demographics, past-medical history details and blood test results of each patient.

BMI: body mass index; DM: diabetes mellitus; PAD: peripheral artery disease; CAD: coronary artery disease; HT: hypertension; AF: atrial fibrillation; ABI: ankle brachial index; DSA: digital subtraction angiography; CTA: computed tomography angiography; CRD: chronic renal disease; HL: hyperlipidemia; COPD: chronic obstructive pulmonary disease; CVD: cerebrovascular disease; Hb: hemoglobin; WBC: white blood cells; Neu: neutrophils; PLT: platelets; MPV: mean platelet volume; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; Cr: creatinine; Ur: Urea; Na: sodium; K: potassium; ALT: alanine transaminase; AST: aspartate transaminase; CK: creatine kinase; LDH: lactate dehydrogenase; Chol: cholesterol; Trig: triglycerides; LDL: low-density lipoprotein; HDL: high-density lipoprotein; INR: international normalized ratio; APTT: activated partial thromboplastin time; PT: prothrombin time; HbA1C: hemoglobin A1C; cm: centimeter; kg: kilogram; m: meter; μ l: microlitre; fl: femtolitre; mm: millimeter; h: hour; IU: International Units; L: Litre; mmol: millimole; U: units; dL: deciliter; sec: second.

i.

Stage	Grade			
	0	I	II	III
A	0	3	0	0
B	0	28	16	3
C	0	30	10	
D	0	8	4	1

ii.

	Ischemia 0				Ischemia 1				Ischemia 2				Ischemia 3			
	W0	W1	W2	W3	F0	F1	F2	F3	F0	F1	F2	F3	F0	F1	F2	F3
	1	14			6	1			2	15	4		2	12		
		2	5	2			3			1	2			1	1	
				1							1					
	F0	F1	F2	F3	F0	F1	F2	F3	F0	F1	F2	F3	F0	F1	F2	F3

Table 2. i. Patients categorized according to Texas Wound Classification system.⁶

ii. Patients categorized according to Wound Ischemia Foot infection Classification system,⁸ (W: wound; F: foot infection).

		Mean	Std. Deviation	Std. Error Mean	P values
Pair 1	Leisure after 12-month follow up	45,8796	21,04544	2,02510	
	Leisure at 1st examination	29,0741	16,74643	1,61143	,000
Pair 2	Physical health after 12-month follow up	45,3704	19,55944	1,88211	
	Physical health at 1st examination	35,3704	17,23536	1,65847	,000
Pair 3	Daily activities after 12-month follow up	46,4815	21,16092	2,03621	
	Daily activities at 1st examination	35,3704	19,39149	1,86595	,000
Pair 4	Emotions after 12-month follow up	40,4861	21,45539	2,06455	
	Emotions at 1st examination	22,7083	16,58004	1,59542	,000
Pair 5	Treatment after 12-month follow up	45,1968	22,32484	2,14821	
	Treatment at 1st examination	33,1019	18,05081	1,73694	,000

Table 3. Quality of life assessment in all domains at baseline (1st examination) and at 12-month follow up.

Self-management				
First examination		After 12 month of follow up		
Mean Self-examination per week	1.84	Mean Self-examination per week	8.4	p< 0.05
Mean Foot washing per week	3.9	Mean Foot washing per week	7.8	p< 0.05
Mean foot hydration per week	0.66	Mean foot hydration per week	7	p< 0.05
Cutting nails		Cutting nails		
Him/herself	64% (66/103)	Him/herself	11.6% (12/103)	p< 0.05
Other	34% (35/103)	Other	70.9% (73/103)	p< 0.05
Specialist	2% (2/103)	Specialist	17.4% (18/103)	p< 0.05
Sock selection	11.6% (12/103)	Sock selection	79.6% (82/103)	p< 0.05
Special anatomical shoes		Special anatomical shoes		
No	92.2% (95/103)	No	80% (83/103)	ns
Walking barefoot:		Walking barefoot:		
Yes	42.7% (44/103)	Yes	7.6% (8/103)	p< 0.05
Visual analog scales				
Mean VAS ADL	6.8±2.5	Mean VAS ADL	4.2±1.2	p< 0.05
Mean VAS INT	6.3±2.2	Mean VAS INT	2.8±1.3	p< 0.05

Table 4. Hygiene self-management assessment between the first and the last examination (12 months) of follow up. A 10 cm visual analogue scale for the impact of pain on daily living activities of (VAS-ADL) (0–10) and a 10 cm visual analog scale for the pain intensity (VAS-INT) (0, no pain; 10, unbearable pain. ns: not significant.

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Oral presentations:

I. XXIII Mediterranean Congress of Angiology and Vascular Surgery, MLAVS 2013, 3-5 of October. Volos, Greece.



Diabetic foot ulceration in Central Greece, preliminary experience from a multidisciplinary team-care approach.

II. 64th European Society for Cardiovascular and Endovascular Surgery. ESCVS 2015, 26-29 of March, Istanbul, Turkey.



A survey on the status of the management of diabetic foot in the Mediterranean region.

III. XXV Mediterranean Congress of Angiology and Vascular Surgery, MLAVS 2015, 22-24 of November, Ljubljana, Slovenia.



Validation of the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) questionnaire and its correlation with visual analog pain scales in Greek population.

IV. 65th European Society for Cardiovascular and Endovascular Surgery. ESCVS 2016, 21-24 of April, Belgrade, Serbia.



Factors associated with healing process in diabetic patients with foot ulceration and evaluation of Quality of life.

Part D

1. Abstract- General Discussion

According to the World Health Organization (WHO), it is possible to encompass all foot complications in the term diabetic foot ulcer (DFU) that has been defined as “ulceration of the foot associated with neuropathy and different grades of ischemia and infection. Nowadays, it is apparent that DFU is a worldwide problem with a great impact on health care cost, the quality of life of the patient and its social environment and finally on the mortality and morbidity of those patients. Within this context we undertook a prospective non-randomized cohort study on consecutive diabetic patients with foot ulcer, to assess factors associated with the healing process or limb salvage, and evaluated the impact of their treatment on their quality of life (QOL).

At the beginning, we conducted a survey under the auspices of the Mediterranean League of Angiology and Vascular Surgery (MLAVS) in order to highlight the current trends in the management of diabetic foot among Vascular Specialists practicing in the Mediterranean region.

From this first publication it was shown that most of the amputations were performed in tertiary hospitals, probably because diabetic foot is by far one of the worse complications in diabetic patients requiring dedicated vascular services that may not be available in small size hospitals in the Mediterranean region. Even in the tertiary hospitals specialists involved with the treatment of diabetic foot were more experienced among their colleagues. Additionally, it was shown that vascular services involved in the management of diabetic foot patients had expertise in both endovascular and surgical skills (open, endovascular and hybrid), while specifically hybrid procedures were associated with lower rate of amputations. This reiterates that vascular services treating diabetic foot should be able to apply all types of interventions to optimize the outcomes.

Another important finding of our study regarding the clinical assessment was the lack of complete clinical evaluation. Although ankle brachial index (ABI) has been recognized as a powerful tool for the detection of peripheral arterial disease, surprisingly it was underused by the vascular specialists responded to our survey. Additionally, only 60% of the vascular physicians considered as important to evaluate the patients for the presence of peripheral neuropathy before the treatment, although it

is known that this can predict the risk of developing a diabetic foot ulcer or higher rate of amputation.

Finally in this study, it was demonstrated that most of the vascular physicians had not adopted a multidisciplinary approach in the management of patients with diabetic foot as a routine in daily practice. This fact shows clearly that at least in the Mediterranean region the multidisciplinary approach of diabetic foot patients is not part of the standard care. Therefore, it appears that reorganization of the service provided to diabetic patients is of paramount importance in the healthcare system of the Mediterranean countries.

In the second publication, we applied the Greek version of the LANSS (Leeds assessment of neuropathic symptoms and signs) questionnaire on patients with diagnosed (neuropathic pain) NP and assessed its validity. Additionally we investigated any association of LANSS with visual analog pain scales (VAS-ADL and VAS-INT). As a result, correlations of test-retest evaluation were statistically significant for total LANSS score as well as for questionnaires' items. The Greek LANSS proved to be a valid instrument for NP assessment, since total score was strongly correlated with the type of pain; neuropathic pain group had significant higher LANSS scores; while the sensitivity and specificity of were 94.29% and 88.57% respectively. In addition, it was

clearly shown that there was a significant correlation between LANNS score and VAS-ADL while there was no such relation noticed for VAS-INT. Thus patients with higher LANNS score (in our case diabetic patients), answered that their pain had a greater impact on daily living activities, although the severity of the pain (VAS-INT) did not differ from that of patients with nociceptive pain. This fact could suggest that NP may have a great impact on quality of life of diabetic patients and their daily activities, although this phenomenon is not always associated with the intensity of the pain.

After the completion of follow up of all participants, in our third publication, we assessed the factors which were associated with the healing process or limb salvage, and evaluated the impact of their treatment on their quality of life (QOL). Firstly, it was demonstrated that patient with diabetic foot ulcer have an inadequate awareness about the nature of the disease. Almost half of our patients presented to our service late from the onset of the ulcer (mean time 24 days), with a poorly controlled diabetes mellitus (DM) (mean Hb1AC: 8.1% and BMI: 28) and low awareness of hygiene self-management. It is true that such patients may neglect themselves because of various reasons including impaired sensation due to neuropathy, impaired vision as a result of retinopathy, and other co-morbidities including cardiac and renal

impairment which all may contribute also to the lack of a personal alarm system. However, it would seem advisable to implement strategies oriented towards the improvement of primary care physician awareness of diabetic foot and its complications, along the recommendations that healthcare professionals should receive periodic education to improve the care of high-risk individuals. After follow up, it was shown that the regular consultations of the patients by their physicians, led to an improvement of their hygiene self-management status considerably, decreasing the likelihood of a new ulcer.

It is still debatable whether ulcer healing in diabetic patient always requires revascularization. In our study no differences were observed in respect to healing rate, minor and major amputation according to the type of intervention. Even in patients who were not considered candidates for revascularization, a reasonable healing rate was observed (46%, 31/67). However, this was an observational study and not designed to compare those treatments.

Additionally, in our study it was demonstrated that initial clinical evaluation with the use of DFI score and TEXAS classification might help physicians to identify which patients are at increased risk for non-healing ulcers or even limb loss, and in whom closer follow up and more aggressive treatment may be indicated. Texas classification, history of

COPD and LANS score may also contribute to the identification of patients with high risk of minor amputation, while delay of hospital referral, the severity of PAD, and the prolonged hospitalization might identify those patients with high risk of major amputation.

We have also underlined the importance of cardiovascular disease risk factor control as primary prevention in patients with DM 2 as it has been recommended from the American Heart Association and the American Diabetes Association. Thus, the majority of deaths in our cohort were cardiac related.

Our study is the first to our knowledge that evaluates the QOL in the same group of patients before and after treatment. Thus, the presence of diabetic foot ulcer was associated with poor QOL, and QOL was significantly improved in all domains of throughout the cohort of our patients after the ulcer management. However, it was interesting, that QOL was improved regardless of patient outcome (healing, minor or major amputation) and no outcome was superior to another. Similarly, VASs were improved after treatment in our cohort. Even in cases that a major amputation was undertaken, the patients perceived their situation as improved in terms of QOL.

In conclusion, during past 4 years, our experience suggests that patients with a diabetic foot ulcer should be always assessed holistically

with evaluation and management of intrinsic (health-related) and extrinsic (social-economic) factors. The need for co-operation among physicians and the function of a multidisciplinary diabetic foot team are mandatory. In the near future, a screening program could be organized in our region in order to assess the prevalence of diabetic foot. Additionally, the primary care network should be better organized in order to be capable of direct referrals of diabetic foot patients to tertiary centre, thus no valuable time would be lost during for diabetic foot patients.

2. Summary of study limitations

Finally, it should be acknowledged that our study may be inherent of some potential limitations. In the first publication, the response rate was 37.5%, which means that our results may not absolutely representative for the entire Mediterranean region. This is aggravated by the fact that our results were not analyzed with regard to the national origin of the physicians. Additionally, in this study only vascular physicians had participated, thus the results may be different if other specialties were available to take this survey such as Orthopedics or

General Surgeons. Also, we considered for granted that all patients were under the care of an endocrine-internal medicine physician. Nevertheless, besides these limitations, we still think that our survey provides a valuable snapshot on the current status regarding the management of diabetic foot patients in the Mediterranean region and our findings reiterate those reported in several other studies.

In the second publication, even though there is no widely established theoretical basis for determining sample size or power calculation in questionnaires psychometric validation, our sample size was relative small compared to the other LANSS validation studies. We also excluded patients with mixed pain so that our two study groups would be more homogenous and gave us more accurate results. This was also a limitation, since it could imply a bias of our study. One other potential limitation inherent in our study was the difference in the mean age between patients with NP and nociceptive pain. Nevertheless, it has not been reported any significant association among patients with NP or nociceptive pain and age. Finally, although we did not assess the impact of NP on quality of life with validated questionnaires, Visual Analogue Scales have provided us short information about the influence of NP on diabetic patients' daily activity, which consists a rough approach of quality of life.

Finally, in the third publication, potential selection and treatment biases may exist as about 50% of patients had PAD, because this study was a prospective observational one, in patients referred to the Vascular Service of a tertiary Hospital. However, this reflects the real world practice of a Vascular Service which inevitably is committed to deal with more difficult-to-heal ulcers.
