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FINAL DEGREE PROJECT

CAN FREE FLAP TRANSFER REDUCE THE INCIDENCE OF AMPUTATIONS IN DIABETIC FOOT INFECTION WITH PERIPHERAL ARTERY DISEASE?

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And finally, thanks to my friends who are still bearing with me after all these years.

1 ÍNDEX

2 ABBREVIATIONS

ABI: Ankle-brachial index

ALT: Anterolateral thigh flap

CLI: Critical limb ischemia

CLTI: Chronic limb-threatening ischemia

DFI: Diabetic foot infection

DFS-SF: Diabetic Foot Scale – Short Form

DFU: Diabetic foot ulcer

DM: Diabetes Mellitus

IWDGF: International Working Group on the Diabetic Foot

LEA: Lower extremity amputation

LOPS: Loss of protective sensation

MRSA: Methicillin-resistant Staphylococcus aureus

PAD: Peripheral artery disease

PVR: Pulse volume recording

QoL: Quality of life

SIRS: Systemic inflammatory response signs

SPP: Skin perfusion pressure

SVS: Society for Vascular Surgery

TBI: Toe brachial index

TcPO2: Transcutaneous oximetry

TMA: Standard transmetatarsal amputation

TP: Toe pressure

3 ABSTRACT

BACKGROUND: Diabetic foot ulcer is a frequent complication of Diabetes Mellitus which represents a major health concern worldwide. Most of the patients diagnosed have an infection as well as peripheral artery disease (PAD) concomitantly, which represents a relevant prognostic factor in wound healing.

Currently, revascularization is indicated in most cases, except for a large area of tissue destruction in which treatment only consists of amputation or a palliative approach. On the other hand, recent studies have seen that despite standardized treatment for diabetic foot infection, patients still had infected non-healed wounds after a year of diagnosis and some patients had undergone amputation. As a result, amputation supposes an enormous burden on patients, families, and society with worsening quality of life. Therefore, this study is proposed to avoid amputation and the problems that this entails.

OBJECTIVES: This study aims to compare standardized treatment with free flap transfer in the management of infected diabetic and PAD foot to reduce the incidence of amputations in comparison to standardized treatment.

As secondary objectives, we will assess whether the quality of life improves, the post-treatment complications and if there is a decrease in the recurrence of diabetic foot ulcers.

DESIGN: Multicenter, longitudinal, prospective, randomized, and open-labelled clinical trial, carried out in 2 hospitals in Catalonia.

METHODS: Study subjects will be those diagnosed with diabetic foot infection and PAD. They will be randomly classified in 2 groups of 276 patients. The control group will receive the standardized treatment and the interventional group, in addition to standardized treatment will undergo reconstruction of the foot with free flap transfer. Patients will be followed-up for 3 years. The main study outcome will be the incidence of amputation. Secondary outcomes will include post-treatment complications, recurrence, and quality of life. The main hypothesis will be tested by calculating the relative risk and its corresponding 95% confidence interval.

KEYWORDS: Diabetic foot ulcer, diabetic foot infection, peripheral artery disease, revascularization, incidence of amputation, quality of life, recurrence, post-treatment complication.

4 BACKGROUND

CONCEPTS

Diabetes mellitus (DM) is defined as a metabolic disorder characterized by chronic hyperglycemia associated with alterations in the metabolism of carbohydrates, proteins, and fats, which occurs because of defects in the secretion of insulin or its action or both. This chronic hyperglycemia is related to long-term lesions and dysfunction in several organs, especially in the nervous system, blood vessels, kidneys, heart, and eyes. Symptoms (polydipsia, polyuria, polyphagia, weight loss) may be present, but they are not specific and are often completely lacking. Various pathogenic processes are involved in the development of diabetes, from the autoimmune destruction of β cells to peripheral resistance to insulin action, although the basis is always the deficiency in the action of insulin in its target tissues.

Type I DM only represents 5-10% of all cases. This sort of diabetes is caused by an absolute deficiency of insulin secretion, due to the destruction of β cells in the pancreas. This type can be attributed to autoimmune pathogenesis and some others because of unknown etiology, in which there is no evidence of autoimmunity, and it is classified as idiopathic DM 1. It usually occurs in childhood and adolescence; however, it can appear at any age.

Type II DM represents 90-95% of diabetes cases. This is caused by a combination of insulin resistance and an inadequate compensatory response, with insufficient secretion for such resistance. The risk of developing it increases, among other factors, with age, obesity, and a sedentary lifestyle. It usually starts progressively after the fourth decade of life, although in recent years there has been a notable increase in young people (1).

Globally, the amount of people with diabetes goes from 108 million in 1980 to 422 million in 2014. Prevalence has been rising faster in low and middle-income countries than in high-income countries, especially DM2 (2). Furthermore, despite significant investment in clinical care, research, and public health intervention it has been seen that there is no sign of a reduction in the rate of increase. This could be explained by unhealthy eating, a sedentary lifestyle, obesity, rapid urbanization, and other factors related to economic development that cause the burden of diabetes to continue rising (3).

In Spain, the estimated incidence of diabetes is 11.6 cases/1000 person-years which means around 386.000 new cases of diabetes that appear in the adult Spanish population (4).

Diabetic foot disease is the infection, ulceration, or tissue destruction of the toe which is associated with neuropathy and/or peripheral arterial disease (PAD) of the lower limbs in a person with currently or previously diagnosed with DM. In this way, diabetic foot ulcers (DFUs)

are known not just as an advanced situation where a diabetic person has a complicated lesion but also a considerable risk of ulceration (5).

The overall lifetime incidence rate of DFU is 19-34% with a yearly incidence rate of 2% (6). Therefore, the natural history of DFU can progress toward successful healing or can develop infections that affect more than half of DFUs (7). As a consequence, approximately 20% of moderate or severe diabetic foot infections lead to some level of amputation, where peripheral artery disease independently increases the risk of nonhealing ulcers, infection, and amputations (8).

According to the National Health Survey of Spain referred to the DM population, the amputation rate is around 3 per 1,000 people with diabetes, being approximately double in men than in women (9). Moreover, it has been seen in other studies carried out in Spain an increase in total amputation rate in patients with DM2 (95% of all amputations with DM) at the expense of an increase in minor amputations without changes in major amputations, which are the ones that have the greatest impact on health (10).

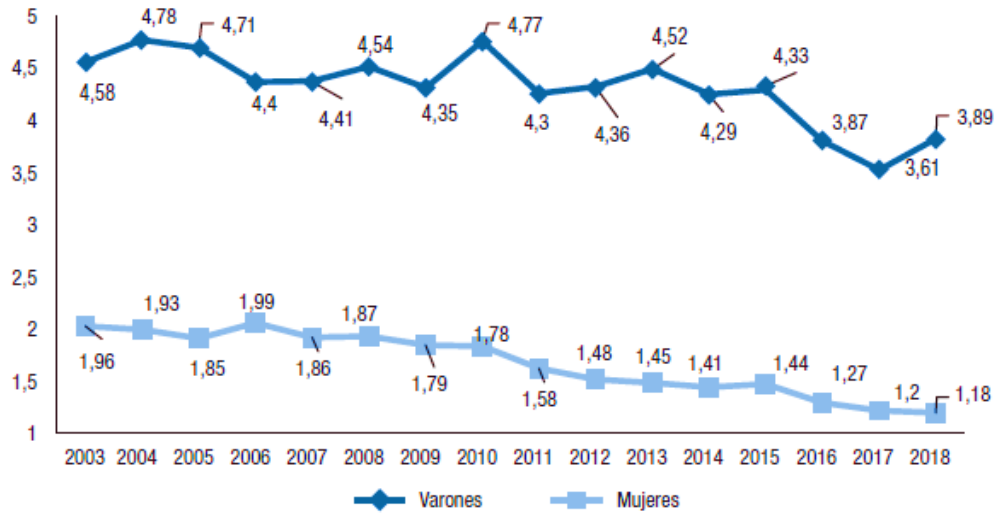


Figure 1: non-traumatic lower limb amputation rate in people with diabetes per 1,000 patients. Spain (2003-2018). Extracted from Diabetic foot approach: diabetes strategy of the National Health System (9)

As a result, amputations are a leading cause of global burden disability and thus constitutes a major public health problem with significant adverse consequences on the healthcare system and health economics (11). Also noteworthy the mortality rate after amputation in long and short term, can be comparable to and even higher than some types of cancers (12). Recently in Spain, it has been estimated that patients with DFU, survival was reduced to 60% at 5 years (13).

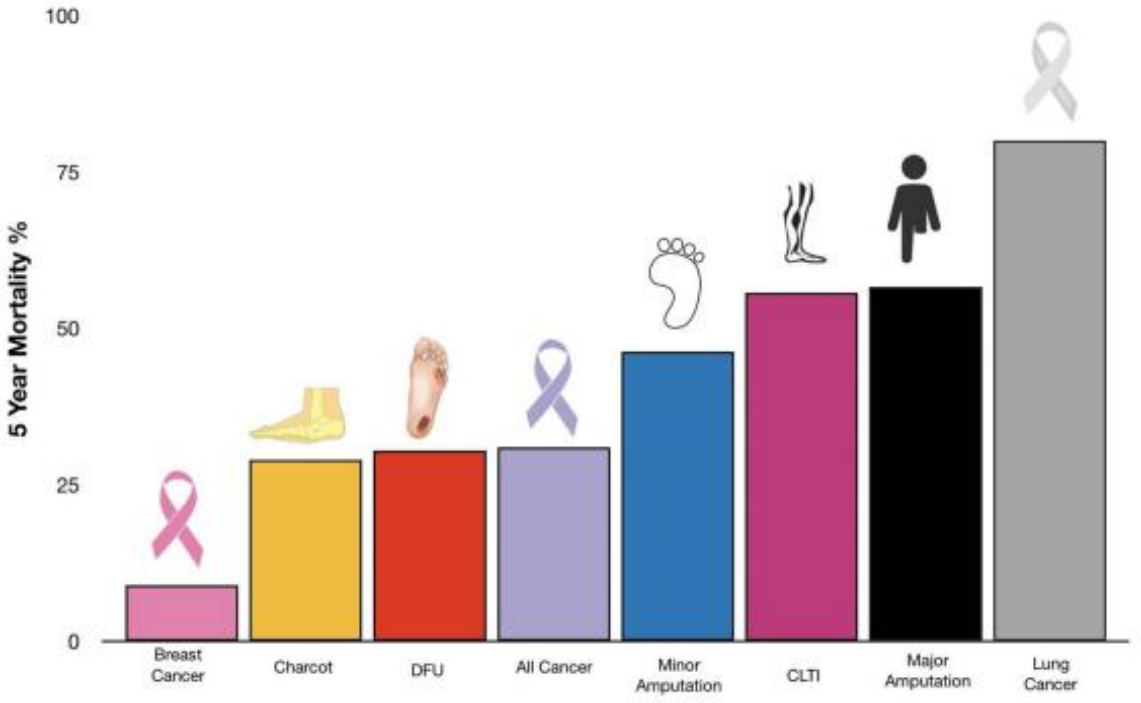


Figure 2: 1 Five-Year Mortality of Diabetic Foot Complications and Cancer. Diabetic foot complications compared to cancer. DFU = diabetic foot ulcers. Charcot = Charcot neuroarthropathy of the foot. All Cancer = pooled 5-year survival of all cancers. CLTI = chronic limb-threatening ischemia. Major Amputation = above-foot amputation. Minor Amputation = foot level. Extracted from (12).

DIABETIC FOOT DISEASE: PATHOPHYSIOLOGY

Diabetic foot disease is among the most serious complications of DM which can lead to major suffering for the patient as well as a considerable burden on healthcare professionals, facilities, and society in general.

The ulcers that are produced in the diabetic feet are frequently a result of a person with diabetes who has simultaneously two or more risk factors. These factors play a significant role in the pathogenesis: peripheral neuropathy, peripheral artery disease, diabetes foot infection, immunological involvement. A summary diagram of the pathophysiology is shown in *Figure 4*.

PERIPHERAL NEUROPATHY

The neuropathy produced by DM is caused by oxidative stress in the nerve cells due to maintained hyperglycemia. Is characterized by being a symmetric eventually, in which motor, sensory and autonomic functions are affected. The peripheral myelin motor fibers can be altered in a length-dependent pattern with the longest nerves affected first, resulting in stocking distribution of sensory/motor loss. Eventually, this ***produces atrophy of the lumbrical and interosseous muscles*** causing changes in the anatomy of the arch foot with an increase in extensor tendon forces which lead to a deformity of the toes like a "claw".

Besides motor fiber dysfunction, sensory loss involving type A myelin fibers causes ***loss of proprioception, pressure, vibratory perception, and impaired gait***. There is also a destruction

of type C sensory fibers causing an ***inability to appreciate painful stimuli***. As a result, diabetic patients can experience repetitive foot trauma without an appreciation of foot discomfort.

Autonomic system dysfunction accompanied by microvascular thermoregulation and anhidrosis causes further ***motor and sensory disturbances***. The ***skin becomes dry and prone to fissuring*** altering its effectiveness as a barrier to microorganism invasion and making it susceptible to dermal infections (14).

For people with neuropathy, minor trauma such as ill-fitting shoes or an acute mechanical or thermal injury can cause ulceration of the foot, acting as a starting *trigger*. In addition, loss of protective sensation (LOPS), foot deformities, and limited joint mobility can result in abnormal biomechanical loading of the foot leading to mechanical stress in some areas. Consequently, the response is usually thickened skin (callus) which can progress to a further increase in the loading of the foot, often with subcutaneous hemorrhage and eventually skin ulceration. Whatever the reason for primary ulceration, continued walking on the insensitive foot impairs the healing of the ulcer (*Figure 3*) (5).

Figure 1. Mechanism of ulcer developing from repetitive or excessive mechanical stress

Figure 3: Mechanism of ulcer developing from repetitive or excessive mechanical stress. Extracted from IWGDF Practical Guidelines (5).

PERIPHERAL ARTERY DISEASE (PAD)

Elevated levels of sugar in the blood create changes in the peripheral arteries, beginning with endothelial cells. This is the most important aspect of microcirculation dysfunction because when there is a disruption in endothelial cells it causes a ***decrease in vasodilator production***, most notably nitric oxide. Consequently, there is persistent vasoconstriction and hypercoagulation which increase plasma thromboxane A2 levels producing a *higher risk of ischemia and ulceration*. Other findings in the endothelium that can be found are signs of reduced local angiogenesis, endocrine cell proliferation, basement membrane thickness, and blood viscosity (15).

Endothelial injury, hyperlipidemia, and the increase of platelet viscosity cause the development of ***atherosclerosis*** in long-term in up to 50% of patients with DFU. The distribution of lower extremity atherosclerosis differs from non-diabetic, typically affecting *infra-geniculate leg arteries* (posterior and anterior tibial arteries) with less common involvement of the aortoiliac artery segment. On the other hand, peroneal dorsalis pedis artery are less involved with atherosclerosis which allows limb revascularization via vein

bypass grafting from popliteal or more proximal artery to restore foot perfusion and achieve ulcer amputation healing.

PAD is an important key factor for impaired wound healing because it decreases the flow of blood to the legs preventing the action of the immunological cascade. In addition, it prevents the optimum delivery of systemic antibiotic, favoring polymicrobial infections and advancement of this.

A small amount of DFU in patients with severe PAD are purely ischemic, these are usually painful and may follow minor trauma. However, the majority of DFUs are either purely neuropathic or neuro-ischemic (5,14).

DIABETES FOOT INFECTION (DFI)

Intervals of poor glycemic control produce immunologic dysfunction with ***impaired leukocyte activity and complement function*** that favors invasive tissue infection. The presence of damaged, or poorly perfused skin and soft tissues ***promote rapid bacteria penetration*** deep into the fascia producing a foot-threatening infection and sepsis. Nature of diabetic foot infection can range from uncomplicated cellulitis to limb and life-threatening necrotizing fasciitis and osteomyelitis.

The etiology of DFI varies by geographic and clinical situation, although *Staphylococcus aureus* (alone or with other organisms) is the predominant pathogen in most cases. Chronical and more severe infections are often polymicrobial (E*nterococcus, Pseudomonas spp.*, staphyl*ococcus, E. coli, Proteus, Klebsiella,…*) as well as the presence of antibiotic-resistant bacterial strains, especially *methicillin-resistant Staphylococcus aureus* (*MRSA*) which is present in 30-40% of cases (14,16).

DFI are a common and serious complication of DFU, with up to 58% of ulcers being infected at early presentation in a diabetic foot clinic, increasing to 82% in patients hospitalized for a DFU (7). These DFIs are associated with poor clinical outcomes for the patient and high costs for both the patient and the health care system (17). Patients with a DFI have a 50-fold higher risk of hospitalization and 150-fold higher risk of lower-extremity amputation compared with patients with diabetes and no foot infection (18).

In this way, as DFI has a poor outcome, early diagnosis and treatment is essential. Unfortunately, systemic signs of inflammation such as fever and leukocytosis are often absent even with a serious foot infection. As local signs and symptoms of infection are often diminished, because of concomitant peripheral neuropathy and ischemia, diagnosing and defining the resolution of infection can be difficult. These deficits, especially in a patient with sensory neuropathy who cannot also sense pain or warmth, might delay awareness of

infection. Amputation, instead of resolution of symptoms or signs of infection, could therefore be a reliable outcome measure in advanced cases (19).

The severity of the infection in DFU with PAD is an important prognostic factor that directly influences the risk of amputation. For this reason, these infections can be difficult to treat and despite the administration of multiple antibiotics the prognosis of clinical resolution can still be poor and as a consequence of repeated courses of antibiotics which can increase risks for antimicrobial resistance (16). A recent study found that one year after diagnosis 55% of DFI patients were still infected and 17.4% had undergone amputation. As a consequence, the treatment of DFI represents a crucial element to avoid further complications (20).

IMMUNOLOGICAL INVOLVEMENT

The immune system of individuals with diabetes is characterized by a reduced healing response in DFUs. For instance, there is an impairment in T-lymphocytes apoptosis, proinflammatory cytokines, degradation of polymorphonuclear cell functions such as chemotaxis, adhesion, intracellular killing, inhibition of fibrocyte proliferation, and impaired basal layer of keratinocytes with reduced migration of epidermal cells. In addition, bacteria such as *S. aureus* flourish at high blood glucose levels (21).

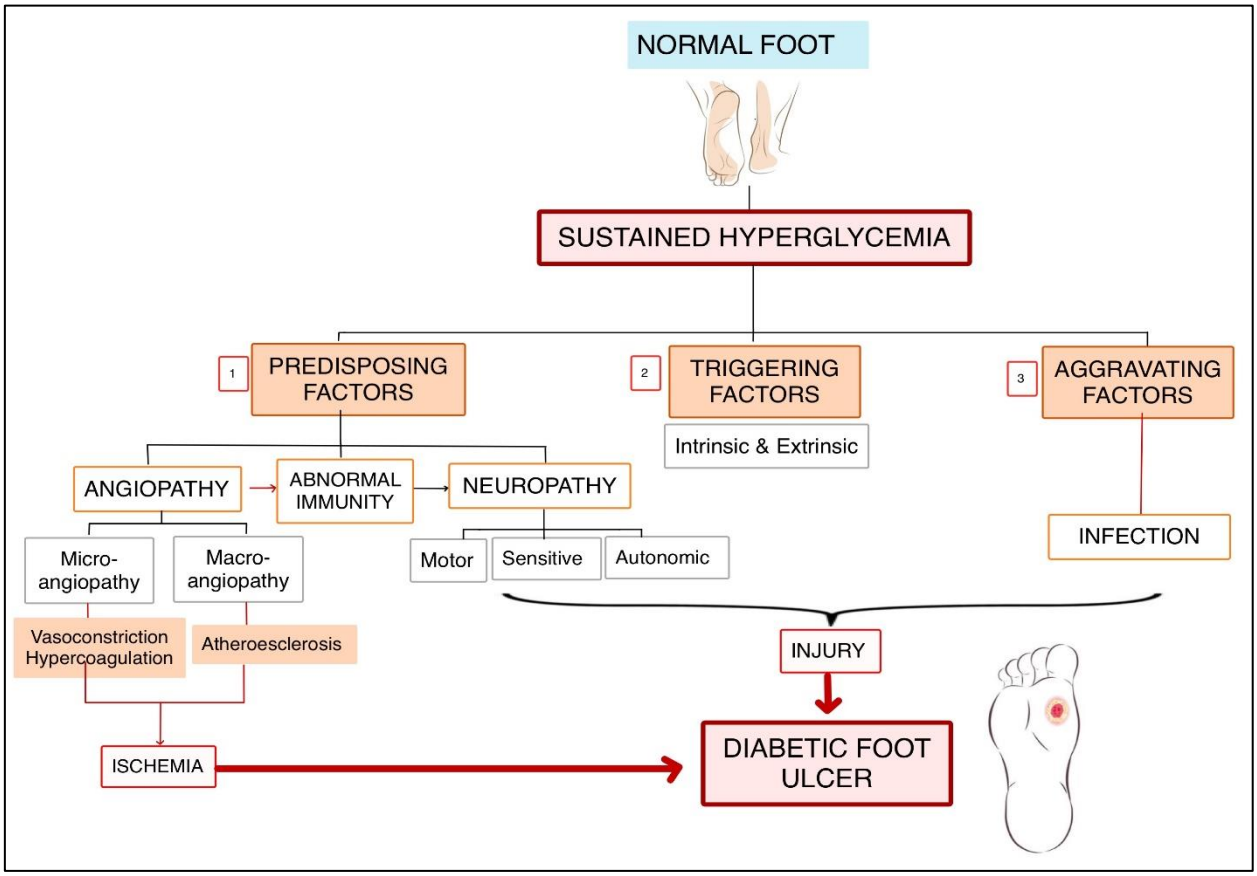


Figure 4: Summary diagram of the physiopathology of Diabetic Foot Ulcers (DFU).

CONCEPTS IN DFU

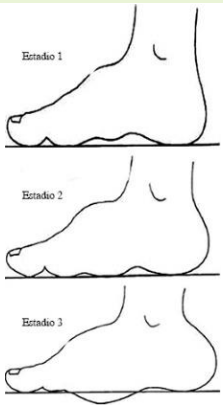
Type	*Definition*	*Diagnosis*
RISK FOOT	The foot of a diabetic person **without injury** but with a probability to present it, depending on the risk factors that the patient has (deformities, neuropathy, ischemia.)	The level of risk is stratified according to (*Table 2*)
DIABETIC FOOT	The Foot of a diabetic person **with an injury.** Can be a consequence of both *microvascular* complications and *macrovascular*.	
NEUROPATHIC FOOT	Characterized by **impaired sensation** with *paresthesia, hypoesthesia*, or *hyperesthesia*. ***Vibratory sensitivity*** is usually the first neuropathic manifestation to disappear, followed by ***distal reflexes*** and, finally, ***tactile***, and ***painful sensitivity → Loss of protective sensation (LOPS).*** Therefore, the alarm symptom that pain implies, is diminished, or canceled, with the consequent risk of not detecting small, repeated rubs, traumas, or injuries that lead to an injury.	LOPS is diagnosed with: -Pressure perception: Semmes-Weinstein 10-gram monofilament -Vibration perception: 128 Hz tuning fork -Test tactile sensation if the other technics are not available: lightly touch the tips of the toes with the tip of your index finger for 1-2 seconds
ISCHEMIC FOOT	Foot injury with the **absence of pulses**. Depending on the degree of ischemia, it will present ***changes*** in ***temperature, coloration, mobility, and sensitivity***. The lesions are usually digital with areas of necrosis.	PAD: Examine arterial pedal waveforms and ankle pressure and ankle-brachial index (ABI), using a Doppler instrument. Excludes PAD: -Triphasic pedal pulse waveform -ABI: 0.9-1.3 -Toe brachial index ≥0.75
NEURO ISCHEMIC FOOT	Lesion in a neuropathic foot with absence of pulses. The main cause of the lesion is neuropathy to which is added, a PAD compensated up to now. It presents neuropathic and ischemic manifestations.	
CHARCOT ARTHROPATHY	Neuropathy-associated syndrome characterized by **fragmentation, bone destruction, and joint** that can produce severe deformities. It could be neurotraumatic or neurovascular (arteriovenous shunts with pulses present). It usually occurs in phases: -Destructuring of the arch without contacting the ground. -Collapse of the longitudinal arch with contact with the ground. -Foot on seesaw.	

Table 1: Definitions in Diabetic foot. LOPS: loss of protective sensation, PAD: peripheral artery disease, ABI: Ankle-brachial index.

IDENTIFYING THE RISK FOOT

The absence of symptoms in a person with DM does not exclude foot disease. They could have asymptomatic neuropathy, PAD, or pre-ulcerative signs. The *International Working Group on the Diabetic Foot* (IWGDF) stablish a ***Risk Stratification System*** which examines the risk of ulceration, including doing the following:

- **History**: previous ulcer/lower extremity amputation, claudication, previous foot education, social isolation, poor access to healthcare and financial constraints, foot pain (with walking or at rest), or numbness.
- **Vascular status**: *palpation of pedal pulses*. However, as clinical examination does not reliably exclude PAD, in most patients it is important to continue the study:
    - **Pedal Doppler arterial waveform:** Detection of triphasic pedal Doppler arterial waveform provide stronger evidence for the absence of PAD.
      Due to medial wall calcification of the arteries in the lower leg which cause rigid arteries, it can lead to elevated ABI, adversely affecting the utility of the test.
    - **Ankle systolic pressure.**
    - **Systolic ankle-brachial index (ABI):** ABI <0.9 is useful for the detection of PAD, although ABI >0.9 does not rule it out. Thus, the following methods must be done.
    - **Toe systolic pressure:** May also be falsely elevated by the same factors as ABI (including digital artery calcification).
    - **Toe brachial index (TBI):** An index ≥0.75 provide stronger evidence of absence of PAD.
- **Loos of protective sensation (LOPS).** Asses with one of these technics:
    - *Pressure perception → Semmes-Weinstein 10-gram monofilament:* Detects loss of protective sensation.
        - Test the three different sites on both feet (*Figure 5a*) ensuring the patient cannot see where the examiner applies the filament. Then, apply the monofilament perpendicular to the skin surface with enough force to cause the filament to bend (*Figure 5b*).
        - The total duration of the approach, skin contact, and removal of the filament should be approximately 2 seconds, and then ask the patient whether they feel the pressure applied (yes/no) and next where they feel the pressure.
        - Repeat this application twice at the same site but alternate this with at least one 'mock' application in which no filament is applied (a total of three questions per site).

- Protective sensation is present at each site if the patient correctly answers on two out of three applications.

- *Vibration perception → 128 Hz tuning fork*: Detects loss of vibratory sensation.
  - Ensure the patient cannot see where the examiner applies the tuning fork. Then, apply the tuning fork to a bony part on the dorsal side of the distal phalanx of the first toe (or another toe if the hallux is absent).
  - Apply the tuning fork perpendicularly, with constant pressure (*Figure 5c*). Repeat this application twice but alternate this with at least one 'mock' application in which the tuning fork is not vibrating.
  - The test is positive if the patient correctly answers at least two out of three applications, and negative if two out of three answers are incorrect.
  - If the patient is unable to sense the vibrations on the toe, repeat the test more proximally (e.g., malleolus, tibial tuberosity).
- *Test tactile sensation*: if the other technics are not available: lightly touch the tips of the toes with the tip of your index finger for 1-2 seconds.

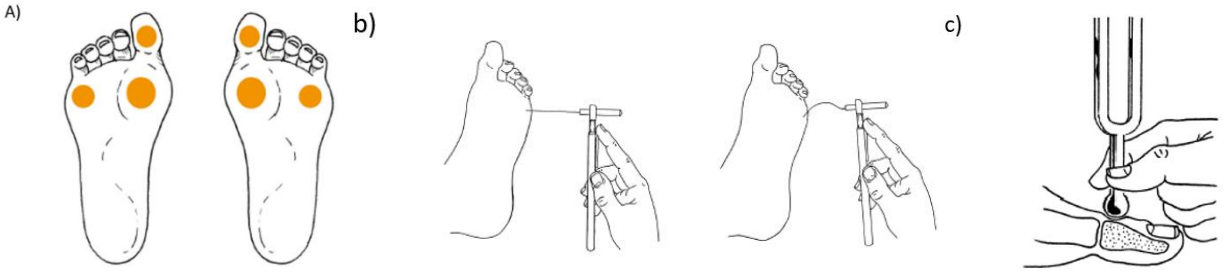


Figure 5: a) Sites that should be evaluated for loss of protective sensation with the 10g Semmes-Weinstein monofilament. b) Proper method of using the 10g Semmes-Weinstein monofilament. c) Proper method of using a 128 Hz tuning fork to check for vibratory sensation. Extracted from (5).

- **Skin**: assessing for skin color, temperature, presence of callus or edema, and pre-ulcerative signs.

- **Bone/joint**: check for deformities (e.g., claw or hammer toes), abnormally large bony prominences, or limited joint mobility. Examine the feet with the patient both lying down and standing up.

- **Footwear**: ill-fitting, inadequate, or lack of footwear.
  - Poor foot hygiene, e.g., improperly cut toenails, unwashed feet, superficial fungal infection, or unclean socks.

- Physical limitations that may hinder foot self-care (e.g., visual acuity, obesity).
- Foot care knowledge.

Following examination of the foot, it can be possible stratify each patient using the **IWGDF risk stratification category system** shown in (*Table 2*) to guide screening frequency. Any foot ulcer identified during screening should be treated (5).

Category	*Ulcer risk*	*Characteristics*	*Frequency**
0	Very Low	No LOPS and No PAD	Once a year
1	Low	LOPS or PAD	Once every 6-12 months
2	Moderate	LOPS + PAD, or LOPS + Foot deformity, or PAD + Foot deformity	Once every 3-6 months
3	High	LOPS or PAD, and one or more of the following: – History of a foot ulcer – A lower-extremity amputation (minor or major) – End-stage renal disease	Once every 3-3 months

*Screening frequency is based on expert opinion, since there is no published evidence to support these intervals.

Table 2: The IWGDF 2019 Risk Stratification System and corresponding foot screening frequency. LOPS: loss of protective sensation, PAD: peripheral artery disease. Extracted from IWGDF Practical Guidelines (5).

In relation to the location of DFU, it has been seen that the spawn point is related to the type of ulcers. In this way, we found:

- Neuropathic ulcers are found in the ***plantar surface*** of toes and ***the plantar metatarsal head region***.
- Ischemic group, in contrast, had the most frequent location in the ***toe tips***.
- *Neuroischemical* ulcers are distributed in both **plantar surface and tips** of the toes (22).

Areas of the foot most at-risk are shown in *Figure 6.*

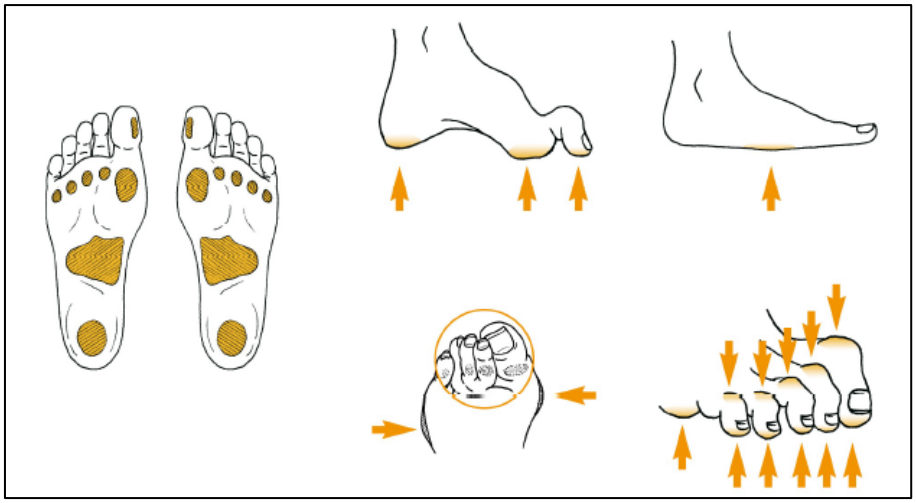


Figure 6: Areas of the foot at highest risk for ulceration. Extracted from IWGDF Practical Guidelines (5).

DIFFERENCES BETWEEN ISCHEMIC AND NEUROPATHIC ULCERS

	ISCHEMIC	NEUROPATHIC
History	Diabetes smoking Arterial hypertension Dyslipidemia	Poor metabolic control Longstanding diabetes Polyneuropathy Charcot arthropathy Biomechanical alterations
Clinical presentation	Slow and progressive evolution Intermittent claudication Intense pain that increases in decubitus or rest and improves with the decline of the tip	Paresthesia, hypoesthesia, corking, burning (*N. sensitive*) Hot, dry skin (N. *autonomic*) Muscle atrophy or weakness (*N. motor*) Little or no pain (*at the level of the ulcer*)
Exploration	absent or weak peripheral pulses ABI < 0.90 Echo-doppler	Sensitivity (superficial/deep) tendon reflexes Peripheral pulses present ABI (> 1.30 vascular calcification)
Presence of gangrene	Extensive	Located
Prognosis	Depending on the degree of ischemia and possibility of revascularization.	Favorable with proper treatment.
Location	Heel Interdigital spaces Lateral edges of the foot Fingertips External malleolus Bony prominences	Pressure areas, especially on the plantar face of the metatarsophalangeal joints, lateral aspect of the ball of the first finger, back of fingers atrophic
Perilesional skin	Fine Shiny Dry Cold, pale, or red (crab skin)	Dry or normal Normal or increased temperature Nice color
Skin appendages	Nail brittleness Onychorrhexis, onychogryphosis, onychomycosis Absence or decrease of hair	Heel cracks (anhidrosis) Onychogryphosis
Ulcer aspect	Irregular with well-defined borders Cyanosis and inflammatory signs	Well defined borders Hyperkeratosis Liquefaction necrosis (maceration)
Size	Small and deep Sometimes there are multiple ulcers	Variable Often single ulcer
Bed of the sore	Absence of granulation tissue Slough and necrotic plaques Atrophic Little exudation	Granulation tissue Cleansed Bleeds easily Moderate/high exudate

Table 3: Clinical differences between ischemic ulcer and neuropathic. ABI: Ankle-brachial index. Extracted from (21).

DIAGNOSIS: CLASSIFICATION SYSTEM OF DFU

The updated *Society for Vascular Surgery (SVS) Lower Extremity Threatened Limb Classification System* that attempts to define the disease burden. The primary purpose of this classification is to provide a more precise description to allow accurate outcomes assessments and comparisons between similar groups of patients and alternative therapies.

Wound healing depends not only on the degree of ischemia but also on the extent and depth of the wound and the presence and severity of infection. Thus, this system dispenses with the term critical limb ischemia (CLI) and instead creates an objective classification of the threatened limb based on the degree of ischemia, wound extent, gangrene, and infection (23).

SVS WIFI CLASSIFICATION SYSTEM

1. **W**ound
2. **I**schemia
3. **F**oot **i**nfection

The WIfI uses a combination of scores for the ***wound*** (based on the depth of ulcer or extent of gangrene), ***ischemia*** (based on ankle pressure, toe pressure, or transcutaneous oximetry), and ***foot infection*** (based on IWGDF/IDSA criteria) to provide a one-year risk for amputation and one-year benefit for revascularization, both stratified as **very low**, **low**, **moderate**, or **high**.

This has benefits over perfusion pressures by including associated wound and infection criteria to provide a more complete wound overview in revascularization decision-making. Whilst WIfI has not been subject to reproducibility assessment in a DFU cohort, it has impressive reproducibility in a PAD setting (24). It has been validated in only one cohort exclusively of patients with an active DFU but has been shown in multiple validation studies to predict outcomes relevant to this clinical group such as healing, time to healing, need for revascularization, lower extremity amputation (LEA), LEA-free-survival and mortality (25,26).

W: Wound/clinical category

Wound	*DFU*	*Gangrene*
0	**No ulcer** Clinical description: minor tissue loss. Salvageable with simple digital amputation (1 or 2 digits) or skin coverage.	No gangrene
1	**Small**, shallow ulcer(s) on distal leg or foot; no exposed bone, unless limited to distal phalanx. *Clinical description: minor tissue loss. Salvageable with simple digital amputation (1 or 2 digits) or skin coverage.*	No gangrene
2	**Deeper ulcer with exposed bone, joint, or tendon**; generally, not involving the heel; shallow heel ulcer, without calcaneal involvement. *Clinical description: major tissue loss salvageable with multiple (≥3) digital amputations or standard transmetatarsal amputation (TMA) ± skin coverage*.	Gangrenous changes limited to digits
3	**Extensive, deep ulcer** involving forefoot and/or midfoot; deep, full thickness heel ulcer ± calcaneal involvement. *Clinical description: extensive tissue loss salvageable only with a complex foot reconstruction or non-traditional TMA (Chopart or Lisfranc); flap coverage or complex wound management needed for large soft tissue defect.*	Extensive gangrene involving forefoot and /or midfoot; full thickness heel necrosis and calcaneal involvement

I: Ischemia

Hemodynamics/perfusion: Measure **Toe pressure** (TP) or **transcutaneous oximetry** (TcPO2) if **ankle-brachial index** (ABI) is incompressible (>1.3).

Patients with diabetes should have TP measurements. If arterial calcification precludes reliable ABI or TP measurements, ischemia should be documented by TcPO2, **skin perfusion pressure** (SPP), or **pulse volume recording** (PVR). If TP and ABI measurements result in different grades, *TP will be the primary determinant* of ischemia grade.

Ischemia Grade	*Ankle-Brachial Index*	*Ankle systolic pressure (mmHg)*	*Toe Pressure, Transcutaneous oxygen pressure (mmHg)*
0	≥0.80	>100	≥60
1	0.6-0.79	70-100	40-59
2	0.4-0.59	50-70	30-39
3	≤0.39	<50	<30

**Flat or minimally pulsatile forefoot PVR = grade 3.*

fI: Foot infection

Foot Infection	
Grade	*Clinical manifestation*
0	**No symptoms or signs of infection** Infection present, as defined by the presence of at least 2 of the following items: – 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	**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 (e.g., trauma, gout, acute Charcot neuro osteoarthropathy, fracture, thrombosis, venous stasis)
2	**Local infection** (as described above) **with erythema >2 cm**, or **involving structures deeper** than skin and subcutaneous tissues (e.g., abscess, osteomyelitis, septic arthritis, fasciitis), and No systemic inflammatory response signs (as described below).
3	**Local infection** (as described above) **with the signs of SIRS**, as manifested by two or more of the following: – Temperature >38ºC or <36ºC – 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

SVS grades: **0** (none), **1** (mild), **2** (moderate), and **3** (severe: limb and/or life-threatening)

Table 4: Society for Vascular Surgery Lower Extremity Threatened Limb (SVS WIfI) classification system. Extracted from (22). SIRS: Systemic Inflammatory Response Syndrome. PaCO2: Partial pressure of carbon dioxide. Cu/mm: cubic millimeter.

PRINCIPLES OF ULCER TREATMENT

Foot ulcers will heal in most patients if the physician bases the treatment on the principles next mentioned. However, even optimum wound care cannot compensate for continuing trauma to the wound bed, or inadequately treated ischemia or infection. Patients with an ulcer deeper than the subcutaneous tissues often require intensive treatment, and, depending on their social situation, local resources, and infrastructure, they may need to be hospitalized.

PRESSURE OFFLOADING AND ULCER PROTECTION

Offloading is essential in the treatment of ulcers that are caused by increased biomechanical stress. Must include bandage systems, support, or cushioning help to relieve the pressure exerted on the patient's ambulation. It can be achieved with different methods, depending on the lesion and characteristics of the patient; and may be enough with overlapping felts adapted to the foot and the location of the lesion (27).

- The preferred offloading treatment for a neuropathic plantar ulcer is a **non-removable knee-high offloading device,** i.e., either a total contact cast or **removable walker rendered** (by the provider fitting it) irremovable.

- When a non-removable knee-high offloading device is contraindicated or not tolerated by the patient, consider using a **removable knee-high offloading device**. If such a device is contraindicated or not tolerated, consider using an **ankle-high offloading device**. Always educate the patient on the benefits of adherence to wearing the removable device.
- If other forms of biomechanical relief are not available, consider using felted foam, but only in combination with appropriate footwear.
- When infection or ischemia is present, offloading is still important, but must be more cautious.
- For non-plantar ulcers, use a removable ankle-high offloading device, footwear modifications, toe spacers, or orthoses depending on the type and location of the foot ulcer.

Figure 7: a) Knee-high total contact cast. b) Ankle-high cast shoe. C) Forefoot-offloading shoe.

RESTORATION OF TISSUE PERFUSION

Revascularization aims is to restore direct flow to at least one of the foot arteries, preferably the artery that supplies the anatomical region of the wound. However, avoid revascularization in patients in whom, the risk-benefit ratio for the probability of success is unfavorable. It has been shown that the application of revascularization techniques (endovascular or Bypass) in diabetics patients with PAD, has been linked with stabilization and even a decrease in the amputation rate. In addition, it is important to emphasize efforts to **reduce cardiovascular risk** (cessation of smoking, control of hypertension and dyslipidemia, and use of anti-platelet drugs).

The revascularization technique should be selected based on both individual factors (such as morphological distribution of PAD, availability of autogenous vein and patient co-morbidities) and local operator expertise. Pharmacological treatments to improve perfusion have not been proven to be beneficial.

Revascularization technique is currently indicated:

- In patients with either an **ankle pressure <50mm Hg** or an **ABI <0.5** consider urgent vascular imaging and when findings suggest an impaired perfusion, a revascularization technique is indicated. Also, consider revascularization if the **toe pressure is <30mmHg or TcpO2 is <25 mmHg**. However, clinicians might consider revascularization at higher pressure levels in patients with extensive tissue loss or infection.
- When an ulcer **fails to show signs of healing within 6 weeks**, despite optimal management, consider revascularization, regardless of the results of the vascular diagnostic tests described above.
- If **contemplating a major** (i.e., above the ankle) **amputation**, first consider the option of revascularization (5).

Afterward, when considering revascularizing, anatomical information of the patient`s lower extremity must be obtained through **color Duplex ultrasound, computed tomography angiography; magnetic resonance angiography**; or **intra-arterial digital subtraction angiography.** Then, evaluate the entire lower extremity arterial circulation with detailed visualization of below-the-knee and pedal arteries, in an anteroposterior and lateral plane.

The technique used is between **endovascular techniques** or **open surgery (Bypass)**, as the first choice, in patients with PAD and diabetes, is a topic still in debate. There is a general tendency to lean initially by endovascular techniques, although there is no randomized study in diabetic patients supporting this so far.

Most diabetic patients have compromised the infrapopliteal arterial segment, being the tibial arteries the most frequent location of the lesions. From the point of view of revascularization, the latest published guidelines suggest that (28):

- **Endovascular technique:** trend is to start the treatment with it whenever is possible to carry out indistinctly (Bypass or endovascular (29).
- **Bypass technique**: has demonstrated better permeability results in the medium and long term when lesions are in the femoral-popliteal sector and include extensive occlusive lesions. Besides, bypass with autologous vein presents, in all studies, better permeability rates and resistance to infection than the prosthetic material. The great saphenous vein is normally used.

Although in the medium-long term, the permeability primary and secondary of the open surgery (Bypass) is greater than in endovascular treatment, there are no differences in amputation rates (30).

On the other hand, revascularization should not be performed if there is no realistic chance of wound healing, or when major amputation is inevitable. The contraindications are:

- *Comorbidities* that confer a significant risk of peri-operative complications
- *Frail vascularization*
- *Short life expectancy*
- *Poor functional status* or *bedridden*
- *A large area of tissue destruction*
- *End-stage chronic kidney disease*: they have a high risk of extremity loss despite revascularization (31).

TREATMENT OF INFECTION

- *Superficial ulcer* with limited soft tissue (**mild infection**):
    - **Cleanse**, **debride** all necrotic tissue and surrounding callus.
    - Start **empiric oral antibiotic therapy** targeted at Staphylococcus aureus and streptococci (unless there are reasons to consider other, or additional, likely pathogens).

- *Deep or extensive* (potentially limb-threatening) infection (**moderate or severe infection**):
    - Urgently evaluate for the need for surgical intervention to **remove necrotic tissue**, including **infected bone**, **release compartment pressure, or drain abscesses**.
    - **Assess for PAD**, if present consider urgent treatment.
    - Initiate **empiric, parenteral, broad-spectrum antibiotic therapy**, aimed at common gram-positive and gram-negative bacteria, including obligate anaerobes.
    - **Adjust** (constrain and target, if possible) the **antibiotic regimen** based on both the clinical response to empirical therapy and culture and sensitivity results (5).

The severity of the infection in DFU with PAD constitutes a particularly important prognostic factor that directly influences the risk of amputation. The treatment of these patients is multidisciplinary, starting with aggressive treatment to eradicate the etiology of the infection. Is used targeted antibiotic therapy, debridement/ local drainage of lesions, and in this situation, revascularization is added to avoid failure of healing and therefore, limb amputation (7).

In the presence of significant infection, the indication of revascularization is:

- Before purulent lesions, abscesses, or systemic condition, treatment is necessary in two stages, first **drainage and local cleaning** with the treatment of the infection, and in second moment proceed to **revascularization** (32,33).
- Patients who undergo endovascular revascularization, can do it simultaneously, if there is no systemic repercussion of the infection.
- In the case of distal Bypass, it usually takes between *3 to 5 days* to control infection.
- In the case of chronic mummified necrotic lesions, revascularization can be done first and then amputation, verifying that the extent of the amputation can be decreased (in the case of minor amputations) (27).

METABOLIC CONTROL AND TREATMENT OF CO-MORBIDITIES

GENERAL TREATMENT:

- **Optimize glycemic control**, if necessary, with insulin.
- **Promote healthy lifestyle habits**: healthy eating, physical activity, not smoking, abstinence, or moderate alcohol intake.
- Early detection and/or **control of other cardiovascular risk factors**: obesity, hypertension, dyslipidemia, smoking.
- Prevention, early detection, and **control of diabetes complications**: retinopathy, nephropathy, and neuropathy.
- **Treat oedema or malnutrition** if present (5).

PROGNOSIS

DFI is a widespread problem and extremely important in the diabetic foot. Infection facilitates microthrombi formation which leads to greater ischemia, necrosis, progressive gangrene, and ultimately to lower-extremity amputation (LEA). The indication of amputations is defined by the vascularization state and the viable tissue after clearing the infection. For this reason, in non-healing wounds with PAD and extensive loss of tissue, amputation is considered.

Amputations can be minor or major: description detailed in *Table 5*.

MINOR AMPUTATION	Confined in the foot	**Toe Amputation**	Just the removal of one or more toes.
		Ray resection	The removal of one or more toes as well as sections of or the entire metatarsal bone.
		Transmetatarsal amputation	Ray resection of all five toes.
MAJOR AMPUTATION	Those produced below and above the knee	**Symes amputation**	The removal of the entire foot but keeping the fat pad and soft tissue from the heel. In this way, the patient can stand on the residual limb.
		Transtibial amputation	the removal of the lower leg while keeping the knee joint intact and functioning.
		Knee disarticulation	The removal is right through the knee joint.
		Transfemoral	The removal is through the femur, also known as above-the-knee amputation (27,34).

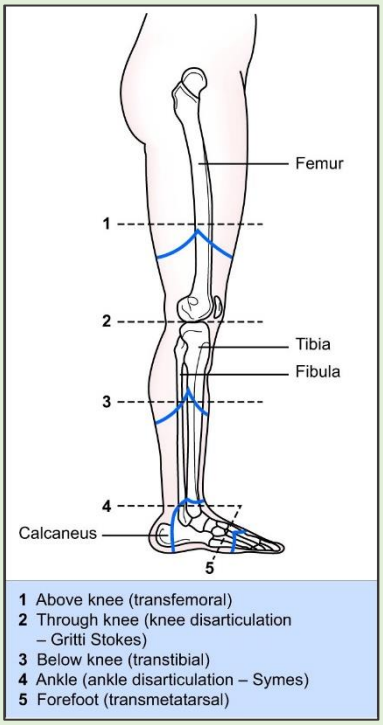


Figure 8: Levels of lower limb amputation. Adapted from Marcovitch, H, Black's Medical Dictionary 2005.

Table 5: Types of amputation.

As a result, amputation related to DM presents an enormous burden on patients, families, and society. Regarding patient limitations, >55% are permanently disabled thereafter which can also affect the psychosocial well-being of the patient. Moreover, those patients who undergo above-knee amputation will never return to a normal ambulatory status because prolonged walking on the residual limb is not recommended due to leg discrepancy that can cause further complications (35,36). For this reason, it also supposes long-term costs associated with protheses, special footwear or other aids, rehabilitation, along with additional costs for home care, social services, and other costs related to any residual disability (37).

On the other hand, studies have seen that more than half (56.6%) of people who had undergone major amputation will be deceased in 5 years, and minor amputation only descends to 46.2% (12,35,36).

FREE FLAP TRANSFER IN DFU

Aggressive treatment of ischemia of the lower extremities has decreased the number of amputations in diabetic patients. Nevertheless, despite vascular reconstruction, the extremity is threatened by an amputation when bone and tendon are exposed due to the extent of the wound (29).

Flap transfer is a more advanced technique where free tissue is transfer for a patient with tissue loss. The ideal flap for reconstruction should provide well-vascularized tissue to control infection, provide an adequate contour for footwear, durability, and a solid anchorage to resist forces. In this way, the combination of both vascular reconstruction with free flap coverage could be a way to prevent a possible amputation. There are some recent retrospective studies where they applied this combined technique and suggested favorable results to prevent amputations in patients with DFU (38,39). *Figure 9* shows a case where this process has been carried out.

Microsurgical free flap reconstruction uses a surgical flap available that meets the needs of the recipient site. These include cutaneous, muscle, bone, fascia, or some combination of these as available options. Proper debridement of the defect must be performed before reconstruction. Pedicle flaps are defined as those in which skin, fat, and muscle are transferred over a vascularized pedicle containing a minimum of one artery and one vein that supply blood flow. With the evolution of plastic surgery, techniques, and the ability to perform microvascular surgery, free tissue transfer allows the design of flaps from remote areas to the foot that can be anastomosed to the anterior or posterior tibial artery and the dorsalis pedis vein or other with similar characteristics.

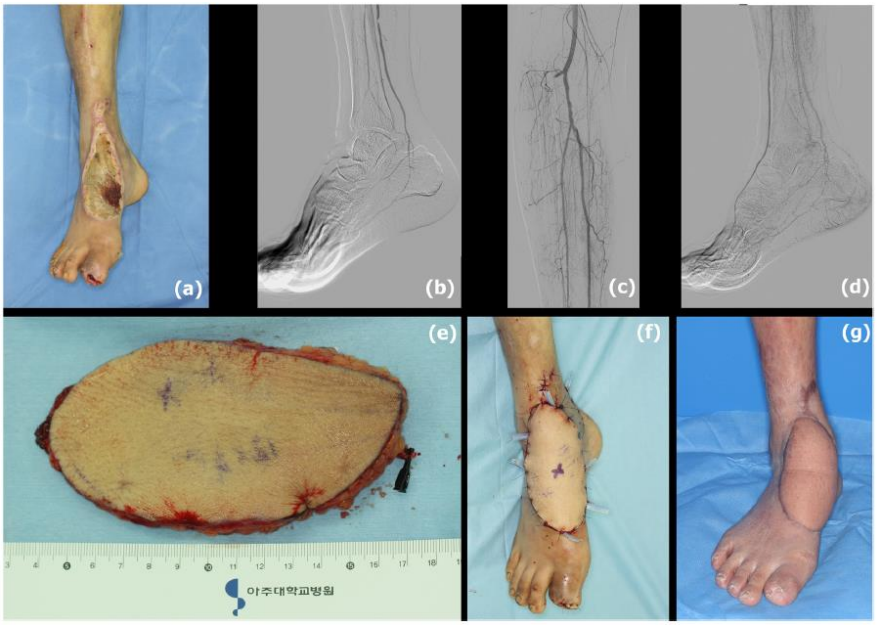


Figure 9: a) A chronic wound of dorsal foot. b, c) Anterior tibial was totally occluded, and pre-operative angiography was indicated of the pedal arch. d) Anterior tibial artery was successfully revascularized and the foot was supplied by both dorsal pedis artery and plantar artery.
e) Anterolateral thigh free flap. f) One day after operating. g) Four months post-operation. Extracted from (39).

ANTEROLATERAL THIGH FLAP (ALT)

There is a variety of flaps obtained from different donor sites that have been described, but the flap choice depends on the size of the defect and the length of the pedicle that is required to reach the defect from the recipient artery (38). This study will focus on the **anterolateral thigh flap** which includes a large and reliable adipocutaneous territory, minimal donor-site morbidity, capability for sensory neurorrhaphy, long vascular pedicle, and the potential for flap thinning with a success rate in adults up to 90% (40).

This flap is based on the descending branch of the *lateral circumflex femoral artery* with a perforator almost always found at the midpoint of a line between the anterior superior iliac spine and the superolateral aspect of the patella and the venous drainage is through one or two concomitant veins accompanying the descending branch of the lateral circumflex femoral artery (41).

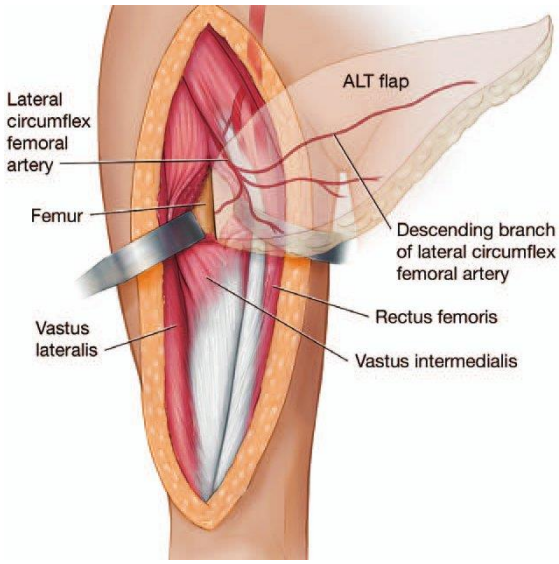


Figure 10: Coronal illustration of the anterior thigh with a pedicle of the Anterolateral Thigh Flap (ALT).

Considering the reconstruction of complex plantar defects, ALT flaps can be designed based on the depth of the wounds. If the wound is superficial, a double-skin paddle flap can be chosen to repair the defect and achieve a good aesthetic outcome (*Figure 11*). For wounds with dead space, vastus lateralis muscle-double skin can be used to repair superficial wounds and fill the dead space simultaneously. In this way, in complex defects of the foot (type III wounds) associated with calcaneal osteomyelitis that historically lead to amputation, the ALT flap allows direct closure of the donor site with full weight-bearing status (42,43).

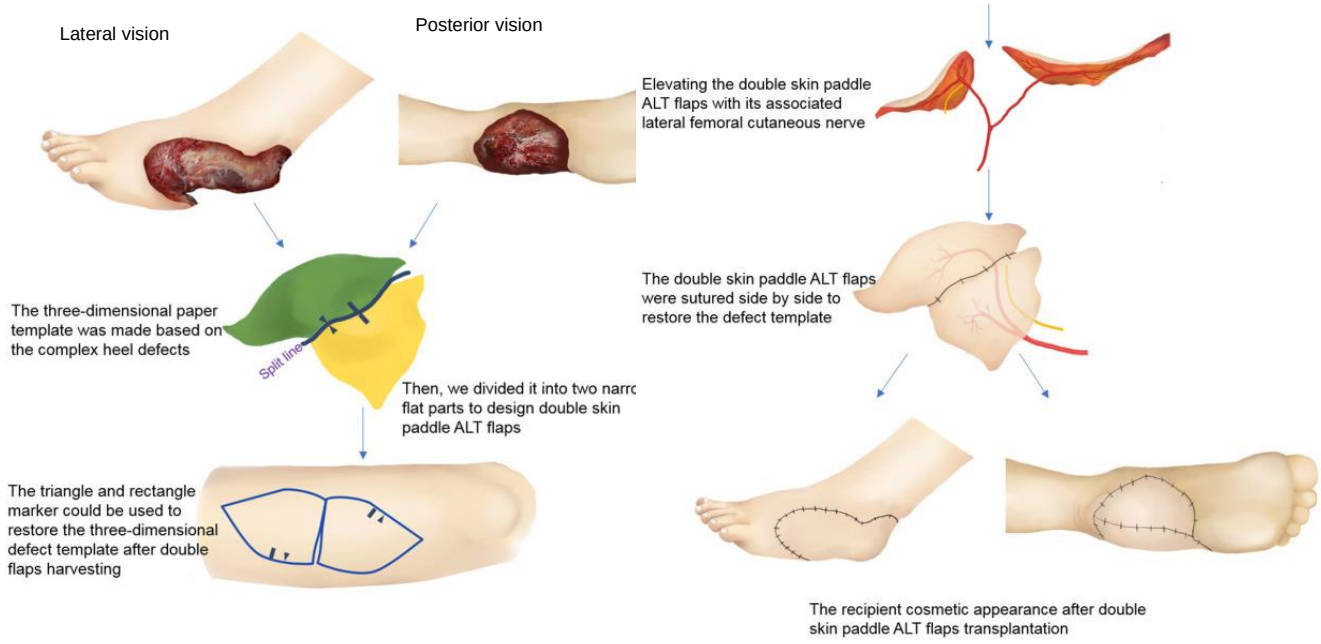


Figure 11: Schematic diagram of double skin paddle Anterolateral thigh flaps (ALT) for complex heel defects. Extracted from (37)

On the other hand, the skin and subcutaneous adipose tissue of the foot and ankle are thin, thus, the flap requires to be thinning to provide a normal fit into footwear. For this reason, the ALT flap is an excellent option since it measures only 3 to 5 mm thick in slim patients. Moreover, overweight patients do not pose any challenge because it is possible to customize thinning to adapt the defect of the foot and ankle (44). The thinned flap also provides superior cosmetic and functional results in areas traditionally difficult to cover with thin, contoured free tissue, like the dorsum of the foot or over the Achilles tendon. When harvesting the thinned ALT flap, caution should be taken to preserve a small cuff of deep fascia around large cutaneous perforators to protect them and their connection to the subdermal plexus (*Figure 12)*, which supplies blood to the skin and superficial layer (45,45).

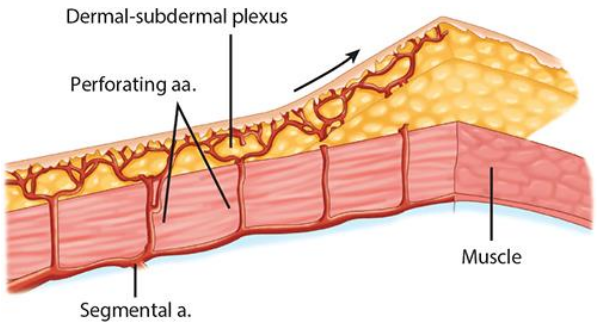


Figure 12: Illustration of a random pattern flap in a transposition rectangular flap. Extracted from Text and Atlas of Wound Diagnosis and Treatment (McGraw-Hill Education)

Subsequently, the flap is checked for vascular viability and then transferred to the defect where is anastomosed one artery and two veins with the help of the surgical microscope. The technique used is 'end to side' to the recipient artery (*Figure 13*), which could be either the *anterior or posterior tibial artery* according to which location is closest to the ulcer. If there were *collaterals* near the recipient artery, these were preserved and not ligated because this can preserve better blood supply to the surrounding tissue and prevents a '*steal syndrome'* (hypoperfusion of the flap distal to the anastomosis) (38,46).

Finally, the donor site on the thigh is closed directly after achieving complete hemostasis, and a vacuum drain is placed under the flap. Skin defects cannot be closed directly in some cases because of the harvest of some deep fascia which allows the muscle to bulge and hinder closure. In these situations, advancing the skin edges and suturing them to the muscle can be done to reduce the size of the defect followed by covering the remaining area with a meshed split-thickness skin graft taken from the medial aspect of the same thigh (46).

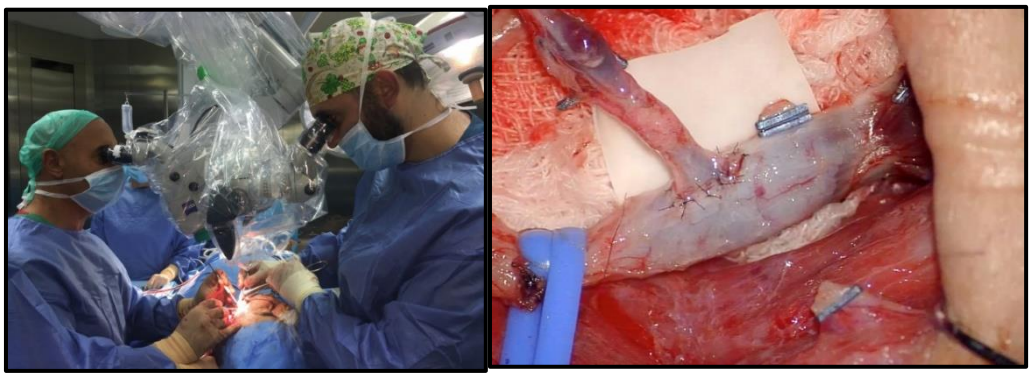


Figure 13: Left image shows plastic surgeons using the surgical microscope to perform the anastomosis. Right image shows the end to side anastomosis.

4.1.1.1 Complications associated to foot reconstruction.

The incidence of complications associated with the reconstruction with free flap is not a negligible issue, where half of the patients face at least one complication of any degree during post-operative period (43). Complications include:

- Wound complications, including infection, seroma, delayed healing, or hematoma.
- Aesthetic complications, such asymmetry, contour irregularities, contracture, volume loss, poor wound healing and scarring.
- Vascular complications, comprising total flap necrosis, venous distress, partial flap necrosis and fat necrosis.
- The skin sensitivity of the reconstructed area will be, at least, diminished or absent.
- Donor site morbidities, including seroma, hematoma, infection, delayed healing. Functional loss is normally negligible, except in very athletic patients (46).

5 JUSTIFICATION

Diabetic foot ulcers (DFU) are a health concern with an overall lifetime incidence rate of 19-34%, of which approximately 58% of ulcers are infected at first presentation (7). It is important to do an early diagnosis and treatment because of the poor outcomes that may result, most importantly, a higher risk of amputation up to 150-fold higher risk compared with patients with diabetes and no foot infection (18). Unfortunately, local signs and symptoms of infection can be diminished because of neuropathy causing the inability of the patient to sense pain or warmth which lead to further progression of the infection and delayed diagnosis (19).

In addition, it is associated with peripheral artery disease (PAD) which also increased amputation risk up to 5-30% (19). All this produces poor clinical outcomes for the patient as well as a worsening quality of life for the patient (17). Currently, revascularization is indicated in most cases, except for large area of tissue destruction in which treatment consists only in amputation or a palliative approach (5). Thus, this study could benefit diabetic foot infection (DFI) providing a new approach that could favor the patient.

On the other hand, the standardized treatment for DFI with PAD consists on cleansing, debride of necrotic tissue, and an antibiotic regimen associated with a revascularization technique (endovascular or Bypass) (5). However, despite this, a recent study found that one year after diagnosis 55% of diabetic foot infection (DFI) patients were still infected and 17.4% had undergone amputation (20).

This study aims to compare the difference between doing the standardized treatment together with free flap transfer in a patient with DFI and PAD and a control group undergoing only the standardized treatment to prove that reconstruction of the foot can increase limb salvage rates in patients with DFI based on previous articles that have been published through the past years (38,39). Those articles were retrospective studies with design limitations since they are less valid than clinical trials. Moreover, they may have sample limitations because it was a in single study center with too few patients. They also had some limitations in the classification system used, since the WIfI classification was not used as suggested in the IWGDF guideline (38). In this way, this study will be designed as a randomized and multicenter clinical trial that will include the recommended classification to minimize bias.

This will be a pioneering study in Catalonia, which will facilitate the extrapolation of the results and help to introduce the free flap transfer in patients with DFI. And in this way, it will contribute to decrease the incidence of amputations and improve the quality of life.

6 HYPOTHESIS

MAIN HYPOTHESIS

Combination of standardized and free flap transfer in the management of diabetic foot infection with PAD will ***decrease the incidence of amputation*** compared to standardized treatment.

SECONDARY HYPOTHESIS

- A combination of standardized treatment and free flap transfer in the management of diabetic foot infection with PAD obtains a ***better quality of life*** during post-treatment period in comparison to standardized protocols.
- A combination of standardized treatment and free flap transfer in the management of diabetic foot infection with PAD causes ***fewer complications during the post-treatment period*** in comparison to standardized protocols.
- The combination of standardized treatment and free flap transfer compared to standardized treatment ***decreases the recurrence*** of further ulcers in patients diagnosed with diabetic foot infection and PAD.

7 OBJECTIVES

MAIN OBJECTIVE:

To compare ***the incidence of amputation*** between the combination of standardized and free flap transfer vs. the standardized management in patients with infected diabetic foot ulcers with PAD.

SECONDARY OBJECTIVES

- To assess whether the ***quality of life during the post-treatment period improves*** by performing the combination of standardized and free flap transfer rather than those treated with standardized protocols of infected diabetic foot ulcers with PAD.
- To ***evaluate post-treatment complications*** in infected diabetic foot ulcers with PAD with the combination of standardized and free flap transfer compared to standardized management.
- To evaluate whether the use of the combination of standardized and free flap transfer compared to standardized treatment causes a ***decrease in the recurrence*** of further ulcers in infected diabetic foot ulcers with PAD.

8 MATERIAL AND METHODS

STUDY DESIGN

This study will be performed as a multicenter, longitudinal, prospective, randomized, and open-labelled clinical trial.

The study will be carried out in 2 hospitals from Cataluña: Hospital Dr. Josep Trueta (Girona) and Hospital Vall d'Hebron. These hospitals are referral centers in Catalonia where the reconstruction surgery can be performed. On the other hand, the recruitment of patients will be supported by the regional hospitals from Girona: Hospital de Santa Caterina, Hospital de Palamós, Hospital de Figueres, Hospital Comarcal de Blanes, Hospital d'Olot i Comarcal de la Garrotxa.

In this way, patients achieved from regional centers will be transferred to a referral hospital if they want to participate in the study. In each referral center, we will assign a principal researcher (diabetic foot unit) who will propose to the patient to enter the study, and then we will select the sample and distribute in two groups. A study coordinator and a statistician will be hired. The first one will coordinate the centers so that they adhere homogeneously to the protocol and obtain good communication and coordination between all of them. The statistician will oversee randomizing and interpret the results of the study.

Both groups will be treated with the standardized treatment and only the interventional group will receive in addition, the free flap transfer.

STUDY POPULATION

The population of this study will be based on patients with DFI and PAD. The patients will be selected and included in the study after having met the inclusion criteria.

INCLUSION CRITERIA

- Patients ≥ 18 years
- Signed consent form.
- DFU >2.5 cm in foot pressure areas or >5cm in any area of no pressure
- Ankle-Brachial index (ABI) <0.5 or Ankle systolic pressure <50 mmHg, or Toe pressure <30 mmHg or Transcutaneous oxygen pressure <25 mmHg .
- When an ulcer fails to show signs of healing within 6 weeks, despite optimal management, regardless of the results of the vascular diagnostic tests described above.
- Foot infection grade ≥ 1 according to the WIfI classification system.

Exclusion Criteria

- Contraindications to revascularization:
    - *Comorbidities* that confer a significant risk of peri-operative complications.
    - *Frail vascularization*.
    - *Short life expectancy*: Life expectancies are calculated using life tables (abridged) presenting age specific mortality rates. Life expectancy tables are calculated based on death probabilities according to ***Farr's death rate method***: *qx = Mx / (Bx + (Mx/2))* where *Mx* = the number of deaths at the age of x to under x+1 years in the reported period; *Bx* = average population aged x to under x+1 in the base period; *qx* = death probability from age x to x+1. Farr's method of calculation of abridged life-tables assumes that there is a constant mortality within the age intervals and thus the years of life lived by a person dying in the interval is (on average) half of the length of the interval (47).
    - *Poor functional status or bedridden*.
    - *Severe chronic kidney disease* (grade 4-5).
- *Non-adherence to antidiabetic treatment*:

  Total of HbA1c where:
    - <7%: adherence to treatment
    - >7%: noncompliance of antidiabetic treatment
- Any patient with *uncontrolled hemorrhagic diathesis or coagulopathy*.

Withdrawal of Patients

Every effort should be done within the bounds of safety and patient choice so that each patient completes the study. Patients who start the follow-up should continue to be followed for 3 years unless there is a justified reason. Motives for patient removal from the study include:

- A request of the patient or the patient´s legal representative.
- Patients who want to do the reconstruction and/or the follow-up in another hospital.
- Patient lost to follow-up. A patient should be considered lost to follow-up only after multiple efforts to contact the patient and after the failure of the patient to attend scheduled visits.
- Case of death.

A record of the patients that leave the study should be noted with their documents as well as the reason.

Sampling

Sample Selection

The sample selection will be conducted in the following hospitals:

Referral hospitals

- Hospital Universitari Dr. Josep Trueta (HUJT)
- Hospital Universitari de Vall d'Hebron (HUVH)

Regional hospital

- Hospital de Santa Caterina
- Hospital de Palamós
- Hospital de Figueres
- Hospital Comarcal de Blanes
- Hospital d'Olot i Comarcal de la Garrotxa

The sample selection will be consecutive, expecting a response rate of more than 50% of the patients. Patients with a recent diagnosis of DFI who meet the inclusion criteria will be considered eligible to participate in the study.

Sample Size

The sample size has been calculated with the help of the GRANDMO sample size and power calculator (version 7.12). Considering the literature published so far, the risk of amputation in patients with DFI and PAD treated with standardized treatment is 17.4% and the assumed risk of amputation in those treated with free flap transfer is 9%.

Accepting an alpha risk of 0.05 and a beta risk of 0.2 in a two-sided test, 276 subjects in the experimental group and 276 in the control group are necessary to find a statistically significant difference in the incidence of the primary outcome, which is expected to be 0.09 in the intervention group and 0.174 in the control group. A dropout rate of 2% has been anticipated.

Estimated Time of Recruitment

According to the data provided by the diabetic foot endocrinology unit of the HUJT, in referral hospitals, there are 3 patients per week with diabetic foot and 1-2 patients per week with diabetic foot in regional hospitals. Of these approximately, 70% have diabetic foot infection. Therefore, the approximate number of patients per year would be:

Referral hospitals ≈ 219

- Hospital Universitari Dr. Josep Trueta (HUJT)
- Hospital Universitari de Vall d'Hebron (HUVH)

Regional hospital: referring patients to HUJT and HUVH ≈ 182-364

- Hospital de Santa Caterina
- Hospital de Palamós
- Hospital de Figueres
- Hospital Comarcal de Blanes
- Hospital d'Olot i Comarcal de la Garrotxa

Considering these numbers, to reach our sample size of 552 patients who meet the inclusion criteria, the estimated time for recruitment is about **two years**.

RANDOMIZATION

Once the patients have signed the informed consent, each of them will be randomly assigned to one of the following two groups:

- **Group A – Control group**: The patient will be treated only with standardized treatment.
- **Group B – Intervention group**: The patient will be treated with standardized treatment and free flap technique.

A full description of the studied interventions is reported in the section *Study Variables: Independent variable*.

The assignment of the subjects will be done by a statistician using a computer-based system to do randomization.

MASKING TECHNIQUES

This study will be open-labelled because the doctor must know the procedure that he will perform on each patient. In the same way, the patient will be aware as well of the treatment he/she is receiving. Masking this study is difficult as the surgeon needs to know what to operate on, and the patient will know if surgery has been performed.

Even if it is open-labelled, though, the statistician who will analyze the results, will not be aware of the surgery made in each of the groups with the aim of reducing biases of selection.

STUDY VARIABLES

MAIN DEPENDENT VARIABLE

- **Incidence of amputation**: it is defined as the number of amputation cases that occurred during the development of the clinical trial.
  In the study, it will be determined the cumulative incidence (CI) which provides an estimate of the probability that an individual free of a certain disease develops during a specified period. Since it is a proportion, it is usually given in terms of percentage accompanied by the observation period to be interpreted.

$$CI = \frac{Nº\ of\ new\ cases\ of\ amputations\ during\ the\ follow-up}{Total\ population\ at\ risk\ at\ the\ start\ of\ follow-up}$$

SECONDARY DEPENDENT VARIABLES

- **Quality of life**: Quality of life is frequently cited as, '*the state of well-being, compounded by 2 components: the ability to perform daily activities reflecting physical, psychological and social well-being; and the patient's satisfaction with levels of functioning and disease control''.* It will be measured with the **Diabetic Foot Ulcer Scale- Short Form (DFS-SF),** which is a 29-item questionnaire scored with a five-point Likert-type scale with *minimum possible score* [1] represented the best quality of life and the *maximum possible score* [5] represented the worst quality of life (*Annex 4*). The items are used to compute scores for 6 QoL subscales deemed important to patients with lower-extremity diabetic ulcers: leisure, physical health, medicine effect, daily life/dependence, negative emotions, worried about ulcer/feet, and bothered by ulcer care. This short form proved to have good psychometric properties and showed sensitivity to ulcer changes over time (48,49).

  This questionnaire will be handled to patients and filled in by them the day before the surgery to have a baseline, 1 week after the surgery, 1 month after the surgery, 3, 6 months after, and from here, every 6 months after the surgery until finish the study.
- **Post-treatment complications:** It will be categorized as a dichotomic yes/no variable. It will be obtained from the patient's clinical chart. Main complications include postoperative necrosis, pain, infection or osteomyelitis, dehiscence, and flap failure. If complications exist, they will be specified. It would be considered "post-treatment" the first 3 months after the intervention.
- **Recurrence**: is defined in our study as the reappearance of foot ulcers during the follow-up of patients after 3 years of being treated in our study. The ulcers can appear in the previous location or any other location of the foot. The diagnosis will be made clinically and classified following the SVS WIfI system (*Annex 1*).

INDEPENDENT VARIABLE

Independent variables of this study are the type of intervention being performed:

- **Group A – Control group**: The patient will be treated only with standardized treatment.

Standardized treatment consists of two stages:

STAGE 1:

- **Cleanse, debride all the necrotic tissue** and surrounding callus. Including removing infected bone if osteomyelitis, releasing the compartment pressure, and draining abscesses.
- ***Dressing and off-loading*** technique considering wound characteristics.
- **Start empiric antibiotic oral/parenteral** depending on infection grade and then a **targeted antibiotic** according to sensitivity results.

STAGE 2: Subsequently, they will receive the revascularization treatment:

- Patients will receive **endovascular revascularization** that can be performed simultaneously with antibiotic treatment if there is no systemic repercussion of the infection.
- In the case of **Bypass**, revascularization needs a control infection between 3 to 5 days.

  Specific candidates to Bypass: femoral-popliteal sector lesions and extensive occlusive lesions.

- **Group B – Intervention group**: The patient will be treated with standardized treatment and free flap technique.

They will additionally undergo the surgical planning of foot reconstruction that will be based on the vascularization observed with the color duplex ultrasound and computed tomography angiography which provides anatomic details of blood flow of the flap and the foot. In this way, the surgical team will define the perfusion zones and delineate the flap used for reconstruction. The reconstruction flap used for the surgery will be the *anterolateral thigh flap* where the circumflex femoral artery will provide the vascularization of the flap. The measurements and thickness of the flap will be given according to the depth of the defect in the foot.

Afterward, the flap is checked for vascular viability and then transferred to the defect where will be anastomosed end to end-side to the anterior or posterior tibial artery according to which location is closest to the ulcer. When collateral arteries are presented close to the recipient artery, they will preserve for better blood supply to the surrounding tissue.

Finally, a vacuum drain is placed under the flap and the donor site is closed directly or if it is not possible, advancing the skin edges and suturing them to the muscle will be performed followed by covering the remaining area with a meshed split-thickness skin graft taken from the medial aspect of the same thigh.

Both groups will be followed up during their hospitalization, 1 week after surgery and, at 1, 3, 6 months, and then every 6 months until completing the 3 years of follow-up. During the follow-up, complications of each treatment will be evaluated and reported, with a primary focus on any degree of tissue necrosis. Surgeons will fill out a data collection form (*Annex 3*) in which they will detail the surgical procedure and complications of each patient. In addition, the questionnaires will be distributed to all patients in the follow-up to register patient satisfaction with the reconstructions and Quality of Life (QoL). The results obtained from the questionnaires of each group will be evaluated and compared by the research team.

COVARIATES

	Variable	Type	Category of Values	Instrument of measure
INDEPENDENT	**Free flap transfer**	Dichotomic qualitative	Yes No	
DEPENDENT	**Incidence**	Categorical quantitative	Scoring from 0 to 100	Cumulative Incidence
	Quality of life	Categorical quantitative	Scoring from 0 to 100	DFS-SF questionnaire
	Post-treatment complications	Dichotomic qualitative	Yes No	Data collection sheet (*Annex 3*)
	Recurrence	Dichotomic qualitative	Yes No	
COVARIATES	**Age**	Discrete quantitative	Numerical (years) *from 18*	Data collection sheet (*Annex 3*)
	Sex	Dichotomic qualitative	Male Female	
	Socioeconomic Status	Discrete quantitative	Social classes from I to V	
	Smoking Habit	Dichotomic quantitative	Yes No	
	Comorbidities	Dichotomic quantitative	Yes No	
	Previous amputation	Dichotomic quantitative	Yes No	
	Defect location	Polytomous qualitative	-Plantar surface of the toes -Plantar metatarsal head region -Calcaneal region	
	Defect size	Continuous variable	Numerical	
	Wound Grade	Categorical qualitative	Grade 1 Grade 2 Grade 3	SVS WIfI classification (*Annex 1)*
	Poor foot hygiene	Dichotomic quantitative	Yes No	Physical examination*

*__Poor foot hygiene__ will be evaluated through a physical examination of the foot considering poor foot examination as ≥1 of: improperly cut toenails, unwashed feet, superficial fungal infection, or unclean socks.

Table 5: Description of the dependent, independent variable, and covariates. DFS-SF: Diabetic Foot Scale-Short Form. SVS WIfI: Society for Vascular Surgery Wound, Ischemia, foot Infection.

DATA COLLECTION AND STUDY CIRCUIT

This process will be carried out in the selected hospitals at the same time. All the data obtained will be collected in a common database that will be later analyzed. A data quality control service will be hired to ensure correct data collection.

Period 1: 1st visit.

On the first visit, we will see patients who have been previously diagnosed with infected DFU that meet the inclusion criteria. In this initial consultation we will ask the patient about his entire medical history, and we will also do a general exam and a specific physical examination of the diabetic foot to find PAD and signs of systemic infection:

- *PAD*: to determine the ischemia grade it would be evaluated the following items:
    - ABI, Ankle systolic pressure, Toe pressure or Transcutaneous oxygen pressure, and Toe pressure if ABI is incompressible.
- *Grades of infection*: According to the SVS WIfI classification system (*Annex 1*).

We will evaluate possible contraindications for performing revascularization and foot reconstruction.
In the anamnesis, we will ask if they smoke or take any medication, especially anticoagulants. We will also ask about the current process and associated symptoms (local swelling, erythema, local tenderness or pain, purulent discharge, fever) and other important comorbidities associated. We will review their recent laboratory tests or if no previous test, one will be performed asses: systemic infection, coagulopathy, renal disfunction, and levels of HbA1c.
Once we have verified that the patient meets all the inclusion criteria and none of the exclusion criteria, we will explain the study and its possible benefits. If the patient accepts, he/she will have to sign the informed consent form to be added to the study. During this visit, we must explain the surgical procedure, its possible complications, and the postoperative period of follow-up.

Period 2: preparing the intervention.

Patients included in the study will be randomized into 2 groups: the control group will undergo only the standardized treatment and the intervention group will receive in addition, a reconstruction of the foot with a free flap.

Subsequently, we must extend the study to get anatomical information on the patient's lower extremity for revascularization and reconstruction treatment. In this way, a **Color Duplex Ultrasound** will be performed to get anatomic details and a physiologic assessment of blood flow. Furthermore, a **computed tomography angiography** will be carried out to get more specific information about the state, trajectory, and anatomical relationship of the blood

vessels. In case of allergic reactions to iodinated contrast, **magnetic resonance angiography** could be used instead. Then, surgical planning for reconstruction will be based on the vascularization observed with the previous techniques and the surgical team will define the perfusion zones that will be used.

Period 3: Treatment and follow-up.

Each group will receive its corresponding treatment and they will be followed up periodically. The visits will be scheduled a week after the surgery, one month, three months, and then every six months until the end of the study. In these follow-up visits, it will be evaluated overall limb survival at 3 years after the diagnosis, post-treatment complications, recurrence, and questionnaires of QoL will be conducted. Patients will first fill out the **DFS-SF questionnaire** (*Annex 4*) the day before the surgery to have an approximation of the quality of life before the treatment. Then, patients will periodically fill in the DFS-SF questionnaire to evaluate changes.

	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12
Schedule	1st day	15-30 day	**Treatment intervention**	1 week after surgery	1 month after surgery	3 months after surgery	6 months after surgery	12 months after surgery	18 months after surgery	24 months after surgery	30 months after surgery	36 months after surgery
General physical exam	X											
PAD	X											
Grades of infection	X											
Renal function	X											
Coagulation factors	X											
Level of HbA1c	X											
Color Duplex Ultrasound		X										
Computed Tomography Angiography		X										
Need for amputation								X				
DFS-SF questionnaire		X						X				
Evaluation of complications								X				
Check recurrence								X				

Figure 14: Patient diagram.
PAD: Peripheral artery disease. HbA1: Hemoglobin A1c. DFS-SF: Diabetic Foot Scale- Short Form.

9 STATISTICAL ANALYSIS

The research team, composed of the principal investigators and a professional statistician, will perform the statistical analysis using Statistical Package for the Social Sciences (SPSS) software (version 1.0.0.1406). A 95% confidence interval will be taken, and the results will be considered statistically significant when the p-value is ≤0.05.

DESCRIPTIVE ANALYSIS

The dependent variables (Incidence, quality of life, success rate of healing, postoperative complications, and recurrence) and the qualitative co-variables (gender, poor foot hygiene, and defect location) will be summarized by proportions, stratifying by the groups of the independent variable.

The quantitative co-variables (age, socioeconomic status, smoking habit, comorbidities, previous amputation, defect size) will be summarized using means and standard deviations (if a normal distribution can be assumed) or medians, first and third quartile (if a normal distribution cannot be assumed), and again stratifying by independent variable groups.

BIVARIATE ANALYSIS

The difference of means and medians concerning the quantitative variables will be analyzed using the **student's t-test** and the **Mann-Whitney U**, respectively, the latter will be used in which case our sample does not follow a normal distribution.

The difference in proportions of the qualitative variable between intervention and control will be analyzed by calculating the **relative risk** and its 95% confidence interval (CI).

Afterward, to determine whether there is a correlation between the study and outcome variables, the **chi-square test** of independence will be used for each dependent variable.

The quality of life during the post-operative period measured by the DFS-SF questionnaire of the two groups of intervention will be analyzed with the **Student T-test,** as the data obtained from the questionnaires will be established at 11 different times to progressively assess the changing in quality of life as postoperative period elapses, having a baseline as well.

MULTIVARIATE ANALYSIS

Since it is a randomized study no between-patient baseline differences are expected. Nevertheless, if differences in baseline characteristics are observed we will handle the possibility of *confusion bias* by carrying out a **multivariate regression analysis**.

10 ETHICAL AND LEGAL CONSIDERATIONS

This study will be conducted in compliance with the latest revision of the Declaration of Helsinki - Medical Research Involving Human Subjects (2013).

Before the start of the research, this protocol will be submitted to the ethics committee of the hospitals involved. The project will begin once approval has been received from all committees.

The ethical principles of Beauchamp and Childress will be respected as follows:

- *Autonomy*: all the participants will be informed about the surgical procedure and the objectives of the research clearly and understandably. Additionally, they will be given a written information sheet and a consent form, and only those who have signed it will be included in the study. These documents (see *Annex 2)* will be submitted in advance to the ethics committee for formal approval.
- *Non-maleficence*: patients who meet the exclusion criteria will be excluded from the project, as they would not benefit from the study procedure.
- *Beneficence*: the inclusion criteria have been described with the intention of including the patients who will benefit most from the study procedure.
- *Justice*: all the patients who meet the inclusion and exclusion criteria and who have signed the consent form will be considered equally for participation in the study, ensuring fairness and equality among individuals.

The confidentiality of the participants will be preserved according to the ‘’Reglamento (UE) 2016-679 del Parlamento Europeo y del Consejo, de 27 de abril de 2016, relativa a la protección de las personas físicas en lo que respecta al tratamiento de datos personales y a la libre circulación de datos’’ and the ‘’Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y garantía de los derechos digitales’’. Thus, the data collected Will be anonymized. All data obtained will be entered and processed in a database to which only the research team will have access.

This study will obey the following laws:

- "Ley 41/2002, de 14 de noviembre, básica reguladora de la autonomía del paciente y de derechos y obligaciones en materia de información y documentación clínica."
- "Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y garantía de los derechos digitales".
- "Ley 14/2007, de 3 de julio, de Investigación biomédica".

Finally, investigators will declare they have no conflicts of interest in any aspect of the study.

11 STUDY STRENGTHS AND LIMITATIONS

- As this trial is open-labelled because of the impossibility to mask patients and surgeons, it can lead to a ***detection bias***. To minimize this possible bias, the statistician who evaluates the results will be masked.
- As it is a multicentric trial in which the main intervention is a surgery (operator dependent) we must consider the risk of ***variability*** in the interventions between different surgical teams. To avoid this, all surgeons participating in the study will perform a preparation before the study starts, in this way, everyone can perform the interventions as similarly as possible according to the protocol and they will receive a checklist to perform the same steps for each patient. Furthermore, all hospitals selected to participate in this study are reference hospitals with similar capacities and resources to be able to obtain common results.
- As the surgery are operator-dependent, the personal experience and the ***learning curve phenomenon*** may be an issue that could affect the study results. To avoid these situations, in each hospital the plastic surgeons will have extensive experience performing microsurgery as well as the vascular specialist will have experience conducting endovascular techniques.
- This is a study in which the patient must be followed-up for three years after the intervention where there is always a ***risk of withdrawals***. To minimize losses, this possible effect has been considered when determining the sample needed for the trial, with a 20% of drop-out rate. Furthermore, to avoid withdrawals, telephone calls will be made to patients by the research team when detecting their absences on the follow-up visits and will encourage them to pursue the study.
- One advantage of being a multicentric study, composed of hospitals from Girona and Barcelona is that, if significant results are achieved, they could be easily more generalized.
- As a prospective clinical trial, it will have a ***long duration*** and will be ***expensive***. The larger the duration is, the more expensive it will become. However, it could potentially suppose in the long term an expense reduction in amputation management, avoiding the use of prosthetics and their continued maintenance.

12 WORKING PLAN & CHRONOGRAM

The hospitals that will participate in the study are the Hospital Universitari Dr. Josep Trueta (Girona) and the Hospital Vall d'Hebron (Barcelona) with the recruitment support of the regional hospitals of Girona (Hospital de Santa Caterina, Hospital de Palamós, Hospital de Figueres, Hospital Comarcal de Blanes, Hospital d'Olot i Comarcal de la Garrotxa).

This study will be carried out by a research team composed of the following:

- *1 General coordinator of the study and a co-investigator*: will take care of the elaboration of the protocol and will oversee the study. They will also supervise the data recollection from the study and present them to the statistician.
- *Center coordinator*: the chief of the plastic surgery service of the referral centers included will coordinate patient recruitment, surgeries, and data collection at their center.
- *Diabetic foot unit coordinator*: there will be a member of the diabetic foot unit who will oversee the management of the patient database in the recruitment phase.
- *Professional statistician*: a professional statistician will be hired, who will be responsible for data collection and statistical analysis.

The estimated time of the study will be 6 years and 3 months. It will include 5 main phases:

PHASE 0: November 2022 – January 2023

- Bibliographic research about DFU, its management, and its treatment options.
- Protocol elaboration including objectives, hypothesis, variables, and methodology.

PHASE 1 – Protocol: February 2023- June 2023

- Monthly meetings of the general coordinators.
- Literature and background review.
- Drafting and presentation of the protocol.
- Presentation to the ethics committee of the three hospitals involved.
- Possible modifications to the protocol.
- Acceptance by the ethics committee of the Hospital Universitari Dr. Josep Trueta as the center responsible for the study.
- Agreement of participation by the ethics committee at HUJT and HUVH
- Liability insurance will be contracted.
- Explanation of the study and distribution of tasks. The research team from each hospital will choose a coordinator who will communicate with other centers and organize tasks from their hospital.

PHASE 2 – Surgeons' Training: First week of July 2023

- Surgeons participating in the research will be sent to a one-week training course in which they will practice the application of indocyanine green.

PHASE 3 - Patient Recruitment and Data Collection: July 2023 – July 2028

- Patient sampling and invitation to participate in the study. All eligible patients will be interviewed and adequately, only patients meeting inclusion criteria, and having the informed consent signed, will be included in the sample. They will be randomly assigned to one of the groups of intervention.
- The intervention will be performed, and patients will be hospitalized. An assessment of possible acute complications will be performed every day, during the hospital stay. Also, QoL questionnaires will be filled in by patients from the day before the surgery and a week after the surgery.
- Follow-up visits will be performed periodically and will also include the realization of the QoL questionnaires. These visits will be scheduled a week after the surgery, one month, six months, and then every six months. Furthermore, patients will also have their routine follow-up visits to check for treatment failure. Follow-up visits will last at least 3 years to evaluate overall limb survival at 3-years after the procedure.
- Specialists will record the information collected on the different variables in every visit in the patient's clinical chart and the study database. For written questionnaires, another option will be sending them to the investigator assistant who will fill them in the virtual study database.
- Biannual meetings of the general, center, and diabetic foot unit coordinator.

PHASE 4 - Statistical analysis and interpretation: August 2028 – November 2028

- Meeting with the entire research team at the beginning of the phase.
- Data collection and development of an anonymized database.
- Statistical analysis It will be performed by an experienced statistical. All the information collected will be analyzed according to the variables of our trial.
- Preparation of tables and graphics and interpretation of results.

PHASE 5 - Final report: August 2028 – February 2029

- Bimonthly meetings with the entire research team.
- Possible modifications and drafting of the final report.
- Presentation of the final report to the scientific community.
- Participation in national and international congresses of plastic and reconstructive surgery

A chronogram of the working plan is presented in Figure 15.

TASKS		2022		2023				2024	2025		2026	2027		2028			2029	
		Nov	Dec	Jan	Feb - Jun	July	Aug - Dec	Jan-Dec	Jan-July	July-Dec	Jan-Dec	Jan-Mar	April-Dec	Jan-July	Aug-Nov	Dec	Jan	Feb
S0	Bibliographic research																	
	Protocol elaboration																	
	Ethical evaluation																	
	Insurance																	
S2	Surgeon's training																	
S3	Recruitment																	
	Intervention																	
	Follow-up and data collection																	
S4	Data compilation																	
	Statistical analysis																	
S5	Report Publication																	
	Participation in congress																	

*Figure 15: **Study Chronogram**. **S= Stage.***

13 BUDGET

MATERIAL COSTS

- *Printing*: for a sample size of 552 patients, we will print 2.200 information sheets and x informed consent double-sided sheets at 0,05€ per copy with a total of 110€. Additionally, the DFS-SF questionnaire will be printed, with an estimated cost of 166€ each visit.
- The cost of *standardized treatment* has not been considered because it is already covered by the National Health Care System which includes costs of procedures, treatments, and follow-up of the patients.
- 1 *Microsurgical microscope*, currently plastic surgery team of HUJT and HUVH has it available.
- *Material for the reconstruction surgery*:
    - Infrared camera device for the visualization of Indocyanine Green Angiography (ICGA): the two hospitals which performed the surgery own it.
    - Specific material should be added for each patient: ICG vials, suture thread, and coupler devices for micro anastomosis (*specified in the budget table*).

PERSONNEL COSTS

- We will hire a *biostatistician* to perform the initial randomization and the statistical analysis of the results. Initially, we have estimated 240 hours of work, with a salary of 35 euros per hour. It would cost 8.400€.
- A *study coordinator* to give assessments and coordinate the medical staff.
- A *training course* will be necessary at a cost of 700€ per person.
- It will be necessary 4 Plastic surgeons for every surgery with a total of 14 plastic surgeons in the referral hospitals which perform the surgery as well as the members of the diabetic foot unit. National Health Care System will cover the salaries of the physician.
- *Data quality control and monitoring manager* to help the investigators at coordinating and data quality control and monitoring respectively to oversee all the information collected from each patient. It would cost 40€/patient.

INSURANCE POLICY

- Since it is an invasive clinical trial, we will hire insurance to cover any possible adverse effect that could result from patients' participation in the study. Its estimated cost is 24.000€. The precise cost will be confirmed at the time of the study kick-off once known the changes to the protocol.

TRAVEL AND COORDINATION EXPENSES

Coordination meetings will take place during our clinical trial. The first one will be before the start of the recruitment and the other 5 will be annual during the 5 years of recruitment and follow-up. Nevertheless, all meetings between coordinators of different hospitals will be telematic via videoconference, so no travel expenses are expected.

DIVULGATION COSTS

- Publication fees: 1.000€ to publish in a journal article.
- Inscriptions to congresses: 800€ for national congresses attendance and 1.600€ for international congresses attendance.

ITEM	AMOUNT	COST	SUBTOTAL	
Personnel expenses				
Statistician	240 hours	35€/hour	8.400€	42.780€
Study Coordinator	5 years	500€/year	2.500€	
Training course	14 surgeons	700€	9.800€	
Data quality control and monitoring	552 patients	40€/patient	22.080€	
Insurance				
Insurance policy	1	24.000€/trial	24.000€	24.000€
Material Costs				
Photocopies	15.250 prints	0,05€/page	762,5€	105.602,5€
ICG vials	276	90€	24.800€	
Microsurgery - Suture thread	552	20€	11.040€	
Coupler	276	250€	69.000€	
Divulgation costs				
Publication fees	1 journal	1.000€	1.000€	4.200€
National congress expenses	2 attendants	800€	1.600€	
International congress expenses	1 attendant	1.600€	1.600€	
			TOTAL	**176.582,5€**

14 FEASIBILITY

MEDICAL TEAM

This multicenter study will be done at Hospital Universitari Dr. Josep Trueta and Hospital Vall d'Hebron. The study will be supported by the diabetic foot unit, the plastic surgeon team, a data manager, and a statistical analyst.

Necessary means such as personnel salaries, operation rooms, and follow-ups will be provided by the national health system.

AVAILABLE RESOURCES

All the hospitals in the study have weekly operating rooms for the performance of foot reconstruction and they have the specific equipment available. The material required for this study is the standard material used which is commonly applied in other types of flap reconstructions. On the other hand, the standardized treatment is already used in daily clinical practice.

PATIENTS

Assuming referral of patients from the regional hospitals from Girona and the own patients from Hospital Universitari Dr. Josep Trueta and Hospital Universitari Vall d'Hebron; we approximate on average 492 patients per year of possible candidates, therefore in about 2 years we would reach our sample size.

15 CLINICAL AND HEALTHCARE IMPACT

According to the World Health organization the number of cases of diabetes have been steadily increasing over the past few decades despite clinical care investment, research, and public health intervention. For this reason, it is also expected an increase of diabetic complications including diabetic foot ulcers.

Nevertheless, diabetic foot infection can be developed without notice due to diminished symptoms and local signs causing further progression of the infection if it is not diagnosed and early treated. Furthermore, it has been also seen, that despite correct treatment of the infection there are patients with unhealed and still infected DFU after a year of diagnosis. And not only that, it should be considered that peripheral artery disease is also associated which represents a key factor in wound healing because it produces impaired healing and a greater risk of amputations if it is neither treated along with infection.

If the hypothesis of this study is validated by the results, it would be reasonable to contemplate a change in the current protocol of management in DFI. With these favorable results, patients could benefit from this hybrid technique that can provide a higher expectancy on lower limb survival and subsequently, decrease disability of amputations along with a better quality of life and indirectly, may decrease mortality rates. In addition, it could also benefit plastic surgeons by contributing a new field to cover.

Thus, the final potential benefit could be improving the management of infected diabetic ulcers. Developing a more consistent handling for this complex disease and could lead to a meaningful change in its treatment and all the significant related social and public health implications in long term.

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17 ANNEXES

ANNEX 1: SVS WIFI CLASSIFICATION SYSTEM

Foot Infection *Grade*	*Clinical manifestation*
0	**No symptoms or signs of infection** Infection present, as defined by the presence of at least 2 of the following items: – 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	**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 (e.g., trauma, gout, acute Charcot neuro osteoarthropathy, fracture, thrombosis, venous stasis)
2	**Local infection** (as described above) **with erythema >2 cm**, or **involving structures deeper** than skin and subcutaneous tissues (e.g., abscess, osteomyelitis, septic arthritis, fasciitis), and No systemic inflammatory response signs (as described below).
3	**Local infection** (as described above) **with the signs of SIRS**, as manifested by two or more of the following: – Temperature >38ºC or <36ºC – 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

Ischemia Grade	*Ankle-Brachial Index*	*Ankle systolic pressure (mmHg)*	*Toe Pressure, Transcutaneous oxygen pressure (mmHg)*
0	≥0.80	>100	≥60
1	0.6-0.79	70-100	40-59
2	0.4-0.59	50-70	30-39
3	≤0.39	<50	<30

**Flat or minimally pulsatile forefoot PVR = grade 3.*

Wound	*DFU*	*Gangrene*
0	**No ulcer** Clinical description: minor tissue loss. Salvageable with simple digital amputation (1 or 2 digits) or skin coverage.	No gangrene
1	**Small**, shallow ulcer(s) on distal leg or foot; no exposed bone, unless limited to the distal phalanx. *Clinical description: minor tissue loss. Salvageable with simple digital amputation (1 or 2 digits) or skin coverage.*	No gangrene
2	**Deeper ulcer with exposed bone, joint, or tendon**; generally, not involving the heel; shallow heel ulcer, without calcaneal involvement. *Clinical description: major tissue loss salvageable with multiple (≥3) digital amputations or standard transmetatarsal amputation (TMA) ± skin coverage*.	Gangrenous changes are limited to digits
3	**Extensive, deep ulcer** involving forefoot and/or midfoot; deep, full thickness heel ulcer ± calcaneal involvement. *Clinical description: extensive tissue loss salvageable only with a complex foot reconstruction or non-traditional TMA (Chopart or Lisfranc); flap coverage or complex wound management needed for large soft tissue defect.*	Extensive gangrene involving forefoot and /or midfoot; full thickness heel necrosis 6 calcaneal involvement

ANNEX 2: INFORMATION SHEET AND CONSENT FORM

HOJA DE IMFORMACIÓN PARA EL PACIENTE

TÍTULO DEL ESTUDIO	Can free flap transfer reduce the incidence of amputations in diabetic foot infection with peripheral artery disease?
INVESTIGADOR PRINCIPAL	Zuleima Ortega Marrero
CENTRO	☐ Hospital Universitari Dr. Josep Trueta ☐ Hospital Universitari de Vall d'Hebron

Introducción

Nos dirigimos a usted para informar lo sobre un estudio de investigación en el que se le invita a participar. Este estudio ha estado aprobado por el Comité de Ética e Investigación Clínica.

La intención de este documento es que usted reciba la información correcta y suficiente de forma que pueda decidir si acepta o no acepta participar en el estudio. Le pedimos que lea esta hoja informativa con atención y nos pregunte cualquier duda que le pueda surgir.

Participación voluntaria

La invitamos a participar en este estudio ya que ha sido recientemente diagnosticado con pie diabético infectado y recibirá el tratamiento específico que consistirá en: limpieza de la herida o desbridamiento, tratamiento antibiótico específico, medidas de descarga, revascularización mediante técnica endovascular o Bypass.

Su participación en este estudio es totalmente voluntaria y en todo momento puede decidir NO participar. Si decide participar, en cualquier momento puede cambiar su decisión y retirar el consentimiento, sin que esto suponga un cambio en su atención sanitaria recibida.

Objetivos del estudio

Este estudio pretende contestar a los siguientes objetivos:

Objetivo principal:

- Demostrar si existe una diferencia en la necesidad de realizar amputaciones entre un grupo control que se someterán al tratamiento estandarizado (previamente explicado) y un grupo de intervención que se someterá a una técnica reconstructiva mediante colgajo.

Objetivos secundarios

- Valorar si existe una diferencia en la calidad de vida posterior entre los mismos grupos de pacientes.
- Evaluar la presencia de complicaciones postratamiento en ambos grupos
- Valorar si la técnica de reconstrucción causa una disminución en la recurrencia de úlceras en comparación con el grupo control.

- Evaluar si se reducen los costes a largo plazo en el grupo de intervención en comparación con el grupo control.

Descripción del estudio

El estudio incluirá un total de 552 pacientes diagnosticados de pie diabético infectado.
Para la evaluación de los objetivos se dividirán los pacientes en dos grupos:

- 276 pacientes en el grupo 1: Se les realizará el tratamiento estandarizado
- 276 pacientes en el grupo 2: Además del tratamiento estandarizado se someterán a una técnica de reconstrucción del pie con colgajo.

La asignación de pacientes entre los grupos se realizará de manera aleatorizada, por lo que usted tiene una probabilidad del 50% de entrar en cualquiera de los dos grupos.

Actividades del estudio

Su participación en este proyecto tendrá una duración de tres años, donde tendrá:

- 1 visita previa a la operación, donde recibirá información sobre el estudio, el tratamiento y la cirugía.
- Técnica de revascularización
- Los del grupo 2: cirugía reconstructiva de pie con colgajo
- Visites de seguimiento distribuidas de la siguiente manera: 1 semana después de la cirugía, al cabo de 1, 3 meses y luego cada 6 meses hasta finalizar los 3 años de seguimiento. En todas las visitas se le evaluará el estado de la úlcera inicial y la reconstrucción si fuera el caso, junto con la realización de un cuestionario.

Riesgos y beneficios

La reconstrucción mediante colgajo es una técnica autorizada y realizada como tratamiento.
Se han descrito los siguientes riesgos:

- La piel de la reconstrucción puede presentar una coloración diferente al resto de la piel de la zona del pie.
- La sensibilidad cutánea de la zona reconstruida estará, al menos, disminuida o ausente
- Secuela estética en la zona del muslo debido a la cicatriz visible
- Pérdida funcional, es inapreciable normalmente, salvo en pacientes muy deportistas.

En caso de recibir la técnica de reconstrucción se puede beneficiar de un buen pronóstico funcional del pie con una morbilidad mínima del sitio donante.

Contacto en caso de duda

Si durante la participación del estudio tiene alguna duda o necesita obtener más información puede ponerse en contacto con su cirujano o con el investigador principal.
Se le proporcionará un papel con los datos de contacto.

Protección de datos personales

Tanto los responsables del estudio como el centro de asegurarán del cumplimiento de todos los participantes contemplados en la normativa de protección de datos nacional y europea.

Sus datos serán accesibles solo para los miembros del equipo de investigación y se añadirán a las bases de datos de forma anónima.

CONSENTIMIENTO INFORMADO

TÍTULO DEL ESTUDIO	Can free flap transfer reduce the incidence of amputations in diabetic foot infection with peripheral artery disease?
INVESTIGADOR PRINCIPAL	Zuleima Ortega Marrero
CENTRO	☐ Hospital Universitari Dr. Josep Trueta ☐ Hospital Universitari de Vall d'Hebron

Yo,_____ (nombre y apellidos del participante)

☐ He leído la hoja de información que se me ha entregado sobre el estudio

☐ He podido hacer preguntas pertinentes sobre el estudio

☐ He recibido la suficiente información sobre el estudio

☐ He hablado con el equipo de investigación.

☐ Entiendo que mi participación es voluntaria.

☐ Entiendo que puedo retirarme del estudio en cualquier momento, sin tener que dar explicaciones y sin que repercuta en la atención sanitaria recibida

Recibiré una copia firmada y fechada de esta hoja informativa y del consentimiento informado.

Presto mi conformidad para participar en el estudio, confirmo que he leído la hoja de información y estoy conforme con su contenido.

Firma del participante

Fecha:_____/___/___

Firma del investigador

Fecha:___/___/___

ANNEX 3: DATA COLLECTION FORM

HOJA DE RECOLECCIÓN DE DATOS

Hoja de recogida de datos de las variables demográficas y epidemiológicas de los pacientes participantes en el estudio.

Hospital: _____
Fecha: _____

Marcar con una cruza la opción que mejor se adecúa

1. **Código numérico asignado: _____**
2. **Fecha de nacimiento (día/mes/año):**___/____/___
3. **Género:**
   - Hombre • Mujer
4. **Estado Socioeconómico:**
   - Clase I: Directivos de Administración y de las empresas (excepto los incluidos en la Clase II). Altos funcionarios. Profesionales liberales. Técnicos superiores.
   - Clase II: Directivos y propietarios-gerentes del comercio y de los servicios personales. Otros técnicos (no superiores). Artistas y deportistas.
   - Clase III: Cargos intermedios. Administrativos y funcionarios, en general. Personal de los servicios de protección y cargos intermedios.
   - Clase IV: Trabajadores manuales cualificados o semicualificados de la industria, comercio y servicios; así como del sector primario.
   - Clase V: Trabajadores no cualificados
5. **Hábito tabáquico**:
   - No fumador
   - Ex-fumador: si actualmente hace más de 6 meses que no fuma
   - Fumador: si fuma actualmente o hace menos de dejado de fumar
6. **Otras enfermedades o trastornos concomitantes**
   - Sí • No • Especificar: _____
7. **Amputaciones previas:**
   - Sí • No
8. **Localización de la lesión:**
   - Planta del pie
   - Región plantar de la cabeza metatarsal
   - Región del calcáneo

9. Tamaño de la lesión

- Especificar: _____

10. Mala higiene del pie:

- Si
- No

Complicaciones de la úlcera:

☐ Celulitis. Fecha: _____

☐ Absceso. Fecha: _____

☐ Osteomielitis. Fecha: _____

☐ Gangrena. Fecha: _____

☐ Otros:_____Fecha: _____

Complicaciones vasculares

☐ Sufrimiento venoso. Fecha: _____

☐ Necrosis total del colgajo de reconstrucción. Fecha: _____

☐ Necrosis parcial del colgajo de reconstrucción. Fecha: _____

☐ Necrosis del tejido adiposo del colgajo de reconstrucción. Fecha: _____

☐ Otros:_____Fecha: _____

Otras complicaciones

ZONA RECEPTORA

☐ Infección. Fecha: _____

☐ Dehiscencia. Fecha: _____

☐ Cicatrización lenta. Fecha: _____

☐ Necrosis de bordes de la ferida. Fecha: _____

☐ Otros:_____Fecha: _____

ZONA DONANT

☐ Infección. Fecha: _____

☐ Dehiscencia. Fecha: _____

☐ Cicatrización lenta. Fecha: _____

☐ Necrosis de bordes de la ferida. Fecha: _____

☐ Otros:_____Fecha: _____

COMPLICACIONS ESTÈTIQUES

☐ Irregularidades del contorno. Fecha: _____

☐ Pérdida de volumen. Fecha: _____

☐ Cicatrización hipertrófica. Fecha: _____

☐ Otras:_____Fecha: _____

NECESIDAD DE AMPUTACIÓN

☐ SI Fecha: _____

☐ NO Fecha: _____

Cuestionario de Calidad de Vida

DFS-SF _____/100

ANNEX 4: QUALITY OF LIFE QUESTIONNAIRE: DIABETIC FOOT SCALE-SHORT FORM (DFS-SF)

¿Cómo le han afectado sus problemas de la úlcera en el pie?

SPANISH VERSION

a) Le han impedido practicar sus aficiones y actividades de

ocio:

1= en absoluto
2= un poco
3= moderadamente
4= bastante
5= mucho

b) Le han cambiado el tipo de aficiones y actividades de

ocio:

c) 1= en absoluto
2= un poco
3= moderadamente
4= bastante
5= mucho

d) Le han impedido ir de vacaciones o hacer una salida de fin de

semana:

1= en absoluto
2= un poco
3= moderadamente
4= bastante
5= mucho

e) Le han modificado ir de vacaciones o hacer una salida de fin de

semana:

1= en absoluto
2= un poco
3= moderadamente
4= bastante
5= mucho

f) Le han hecho pasar más tiempo planeando y organizando sus

actividades:

1= en absoluto
2= un poco
3= moderadamente
4= bastante
5= mucho

Debido a sus problemas de úlcera de pie, ¿con qué frecuencia se ha sentido...

g) cansado o fatigado?

1= nunca
2= casi nunca
3= algunas veces
4= casi siempre
5= siempre

h) agotado?

1= nunca
2= casi nunca
3= algunas veces
4= casi siempre
5= siempre

i) con dificultades para dormir?

1= nunca
2= casi nunca
3= algunas veces
4= casi siempre
5= siempre

j) con dolor al caminar o estar de pie?

1= nunca
2= casi nunca
3= algunas veces
4= casi siempre
5= siempre

k) con dolor durante la noche?

1= nunca
2= casi nunca
3= algunas veces
4= casi siempre
5= siempre

Debido a sus problemas de úlcera de pie, ¿con qué frecuencia ha...

l) dependido de otras personas que le ayuden en su cuidado personal?

1= nunca
2= casi nunca
3= algunas veces
4= casi siempre
5= siempre

m)dependido de otras personas para realizar labores rutinarias del hogar?

1= nunca
2= casi nunca
3= algunas veces
4= casi siempre
5= siempre

n) dependido de otras personas para salir de casa?

1= nunca
2= casi nunca
3= algunas veces
4= casi siempre
5= siempre

o) dedicado más tiempo en planificar y organizar su vida diaria?

1= nunca
2= casi nunca
3= algunas veces
4= casi siempre
5= siempre

p) sentido que para hacer cualquier actividad tardaba más tiempo de lo que le hubieragustado?

1= nunca
2= casi nunca
3= algunas veces
4= casi siempre
5= siempre

Debido a sus problemas de úlcera de pie, ¿se ha sentido...

q) enfadado por qué no ha podido hacer lo que a usted le gustaría?

1= en absoluto
2= un poco
3= moderadamente
4= bastante
5= mucho

r) frustrado porqué otros han tenido que hacer algo que a usted le hubiera gustadohacer?

1= en absoluto
2= un poco
3= moderadamente
4= bastante
5= mucho

s) frustrado por qué no ha podido hacer lo que le hubiera gustado?

1= en absoluto
2= un poco
3= moderadamente
4= bastante
5= mucho

t) preocupado por si su úlcera(s) no se curará(n) nunca?

1= en absoluto
2= un poco
3= moderadamente
4= bastante
5= mucho

u) preocupado por si pudiera sufrir una amputación?

1= en absoluto
2= un poco
3= moderadamente
4= bastante
5= mucho

v) preocupado por una posible herida en los pies?

1= en absoluto
2= un poco
3= moderadamente
4= bastante
5= mucho

w) deprimido por qué no ha podido hacer lo que le ha gustado?

1= en absoluto
2= un poco
3= moderadamente
4= bastante
5= mucho

x) preocupado por la aparición de nuevas úlceras en el futuro?

1= en absoluto
2= un poco
3= moderadamente
4= bastante
5= mucho

y)enfadado porqué esto le ha pasado a usted?

1= en absoluto
2= un poco
3= moderadamente
4= bastante
5= mucho

z)frustrado porqué tiene problemas para desplazarse?

1= en absoluto
2= un poco
3= moderadamente
4= bastante
5= mucho

Debido a su problema de úlcera en el pie, ¿con qué frecuencia se ha sentido molesto por...

aa) tener que mantener la úlcera del pie sin tener que cargar peso sobre ella?

1= nunca
2= casi nunca
3= algunas veces
4= casi siempre
5= siempre

bb) la cantidad de tiempo que implica el cuidado de la úlcera del pie?

1= nunca
2= casi nunca
3= algunas veces
4= casi siempre
5= siempre

cc) el aspecto, olor o supuración de la úlcera?

1= nunca
2= casi nunca
3= algunas veces
4= casi siempre
5= siempre

dd) tener que depender de otros para ayudarle a curar la úlcera?

1= nunca
2= casi nunca
3= algunas veces
4= casi siempre
5= siempre

Puntuación total: