Faculdade de Engenharia da Universidade do Porto

Diabetic foot thermophisiology characterization

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"Para mantermos um diabético a caminhar sobre os seus pés há que lhes prestar, nós, ele e os seus familiares mais chegados, todas as atenções. Quase como se fossem de vidro…"

Sociedade Portuguesa de Cirurgia

Abstract

Diabetes affects around 13% of the Portuguese population,one in seven patients are at high risk of developing diabetic foot. This condition involves several anatomopathological and peripheral neurological disorders, which affect the peripheral microcirculation. This might have serious consequences such as: ulcers, ischaemia and amputations. The monitoring and assessment of the treatments are important to evaluate its progression, and to promptly act in case of regression.

Medical thermography is a noninvasive, nonionising, safe and accurate medical imaging method that enables to monitor the temperature distribution on the surface of the skin. This information is directly related to the physiology, allowing for real-time assessment, in particular microvascular peripheral and autonomic nervous systems. The diabetic foot has manifestations in these two systems and is therefore capable of being monitored by the proposed technique.

The present project aims to investigate the use of medical thermography in the physiological characterization of patients who already were diagnosed with diabetic foot. Moreover, this research should result in the definition of a protocol for the collection and analysis of thermographic images of diabetic foot. The results of this project will allow the study of diabetic foot disease more extensively, enabling a better knowledge of its physiology. The potential of thermography as a tool for folow-up of treatments was evaluated. The data collections were perfomed at the Diabetic Foot Clinic at the Hospitalar Center of Porto.

The obtained results can be used as reference for future research studies in the area, the proposed methodology can be improved to become used in daily practice, helping clinical professionals in the diagnosis and treatment assessment, providing better care and reducing the associated costs.

Keywords: diabetic foot; temperature distribution; thermography; ulcers.

Resumo

A diabetes afeta cerca de 13% da população portuguesa, cerca de um em cada sete doentes com diabetes, está em sério risco de desenvolver pé diabético. Trata-se de uma série de alterações anatomopatológicas e neurológicas periféricas que afetam a microcirculação periférica e podem ter como consequências graves: úlceras, isquemias e amputações. Pelo que a caracterização e monitorização destes sistemas é importante de forma a evitar a sua progressão.

A termografia médica é um método de imagem clínica não invasivo, não ionizante e preciso que permite monitorizar a distribuição da temperatura à superfície da pele. Esta informação fisiológica pode ser avaliada em tempo real, monitorizando os sistemas microvascular periférico e nervoso autónomo. O fenómeno do pé diabético tem manifestações nesses dois sistemas e é portanto passível de ser monitorizado por essa técnica.

Este trabalho de investigação tem como finalidade caracterizar a distribuição da temperature à superfície da vista plantar do pé em doentes, bem como o desenvolvimento de uma metodologia para a sua monitorização. O trabalho de campo foi realizado na Clínica do pé diabético do Centro Hospitalar do Porto.

Os resultados deste projeto permitirão efetuar estudos de maior dimensão na área da patologia do pé diabético, possibilitando conhecer melhor a sua fisiologia, auxiliar no diagnóstico e conduzir para um tratamento mais adequado, permitindo a avaliação contínua destes tratamentos. Dessa forma contribui para um aumento da qualidade de vida dos doentes de pé diabético e permite reduzir de forma eficaz os custos associados à patologia.

Palavras-chave: distribuição de temperatura; pé diabético; termografia; úlceras de pressão.

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Abbreviations

ABI	Ankle-brachial index
ANS	Autonomic nervous system
CHP	*Centro Hospitalar do Porto*
DM	Diabetes Mellitus
EU	European Union
IDF	International Diabetes Federation
IR	Infrared radiation
OECD	Organisation for Economic Co-operation and Development
ROI	Region of interest
SNS	*Serviço Nacional de Saúde*
VS	Vascular system

Chapter 1

Introduction

Diabetes mellitus (DM) is a disease characterized by chronic hyperglycemia with disturbances of the metabolism of carbohydrates, fats and proteins resulting from defects in insulin secretion, insulin action, or both. There is a worldwide prevalence of disease due to aging populations, poor diet, concomitant epidemic of obesity, physical inactivity and unhygienic environment [1].

According to the *International Diabetes Federation* (IDF), diabetes affects over 371 million people worldwide, accounting for 8.3% of the world population and continues to increase in all countries. In over 50% of people with diabetes it has not been diagnosed, pursuing their silent evolution [2].

Diabetes in 2012 caused the deaths of 4.8 million people, half of whom were under 60 years, and it is estimated that in 2030 the number of people with diabetes worldwide will reach 552 million, representing an increase of 49% of the population affected by the disease [3].

A report published in November 2012 by OECD, shows that Portugal is the European Union (EU) country with the highest prevalence of diabetes (9.7%), a percentage that exceeds by more than three percent the mean of the EU, as shown in Figure 1 [4].

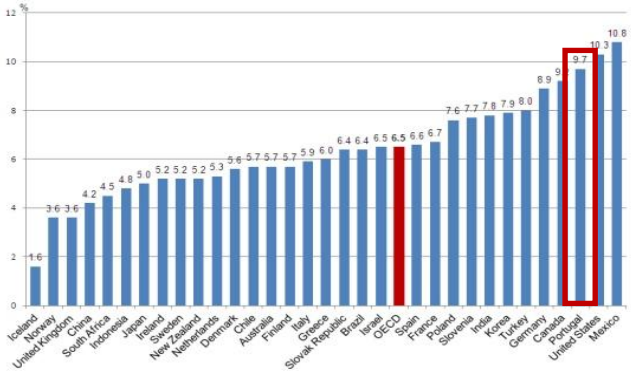


Figure 1 - Distribution of diabetes in many countries worldwide in 2012 [4].

1.1 - Motivation

Diabetes affects 12.7% of the portuguese population aged between 20 and 79 years, which corresponds to an estimated 1.003 million individuals [3].

Pathologic changes associated with diabetes are numerous, and the diabetic foot is one of the most complicated health problems. Diabetic neuropathy affects changes in sensitivity of the feet and is mainly responsible for the appearance of these lesions, which are difficult to treat and to prognosis [5].

Since diabetes is a condition that affects a large number of population, the costs associated with this have great economic impact on the *Serviço Nacional de Saúde* (SNS) and also in the patients self costs. With diabetic population increasing, these costs are also increasing proportionally (Figure 2). It is essential to investigate ways to prevent and deal with diabetes on a cost-effective manner for the general population and the SNS.

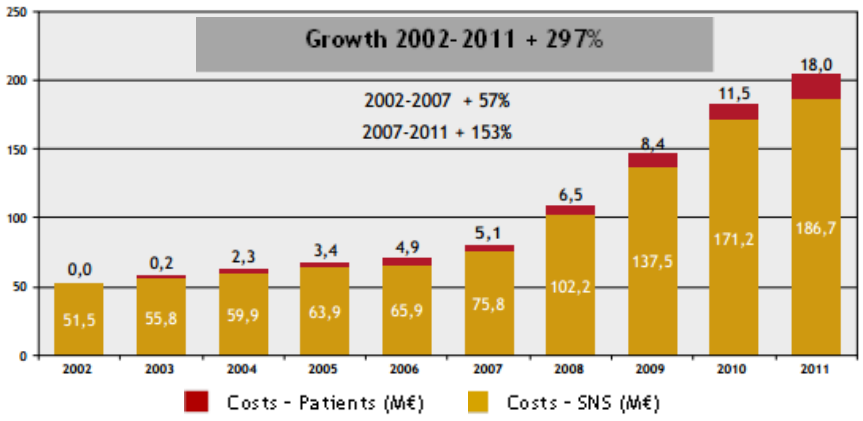


Figure 2 - Number of sales of Insulins and Oral Antidiabetic in Ambulatory within the SNS in Portugal Continental - In Value. (Source: Estatísticas do Medicamento – INFARMED) [3].

However, there are other costs associated with diabetes, such as loss of income, productivity decrease of affected patients and the psychosocial aspect of patients and their families, who despite of being intangible are nonetheless important.

The temperature is a useful indicator of various diseases, the medical use of Thermology techniques, such as infrared-based imaging, has potential of use in medicine [6].

Infrared thermography is a technique that allows mapping the surface temperature of the human body or a region, with the intent of distinguishing areas with different values. Since 1960, there is an increased understanding of the physiology and thermal relation between the skin temperature and blood perfusion. Moreover, the recent advances in the standardization of the technique and the advantages of computer aided medical imaging systems have greatly improved the reliability of this technology in medicine. In diabetology studies it was

demonstrated its value and relevance to the clinical evaluation of peripheral perfusion and tissue viability [7].

Medical thermography provides functional information that is not provided by any other medical imaging methods, and has the great advantage of being non-invasive, non-ionizing and accurate, passively capturing the radiant heat emitted from the human body surface [8,9].

In diabetes, vascular activity in the extremities, especially in the feet, can be indicative of autonomous nervous system activity, because the vasomotor function is regulated by autonomic fibers of the sympathetic system, and its dysfunction could be associated with different patterns of temperature in diabetics [10].

Complications affecting the lower limbs are the most common manifestations of diabetes and infrared imaging can be a useful tool for early identification of those conditions and aid to prevent more serious complications, which can lead to amputations, in the most extreme situation.

Due to the severity of problems that may be related to diabetes, and the fact of this condition is increasingly affecting more people worldwide, it is necessary to develop effective methods to timely detect these situations. Medical thermography presents itself as a very credible solution, since it is a painless, non-invasive, non-ionizing and accurate method, since it does not cause any harm or discomfort to the patient, and is economically affordable [11].

1.2 - Aim

The aim of this research is to develop a methodology for characterizing the skin temperature of the plantar feet in diabetic patients.

In addiction to this main goal, the objectives were:

- Design, implement and assess a methodology for studing surface skin temperature of the plantar feet.
- Characterize the thermal profile of plantar feet in a healthy population.
- Characterize the temperature profile of plantar feet in diabetic feet patients.
- Evaluate quantitative benchmarks to be used as references for future studies.
- Evaluate the proposed methodology for frequent follow-up of diabetic foot patients, through a study case.

1.3 - Structure of the Dissertation

This document is further organized in five sections:

The literature review is divided in two main topics: firstly diabetes is classified and then diabetic foot and its main complications are presented. The other topic is thermography, where the technique is described, the role of thermoregulation and the relevant studies of thermography in the diabetic foot.

Methodology, the images capture protocol, materials and methods used in this research and the analysis methods.

Results, present the outcomes of all the tests and experiments performed, and also its interpretation and more relevant information.

Discussion, analyzes the significance of findings and the justification of the deviations.

Conclusion, states the accomplishment of the aim and the proposed future work.

Figure 3 shows the navigation diagram of this dissertation.

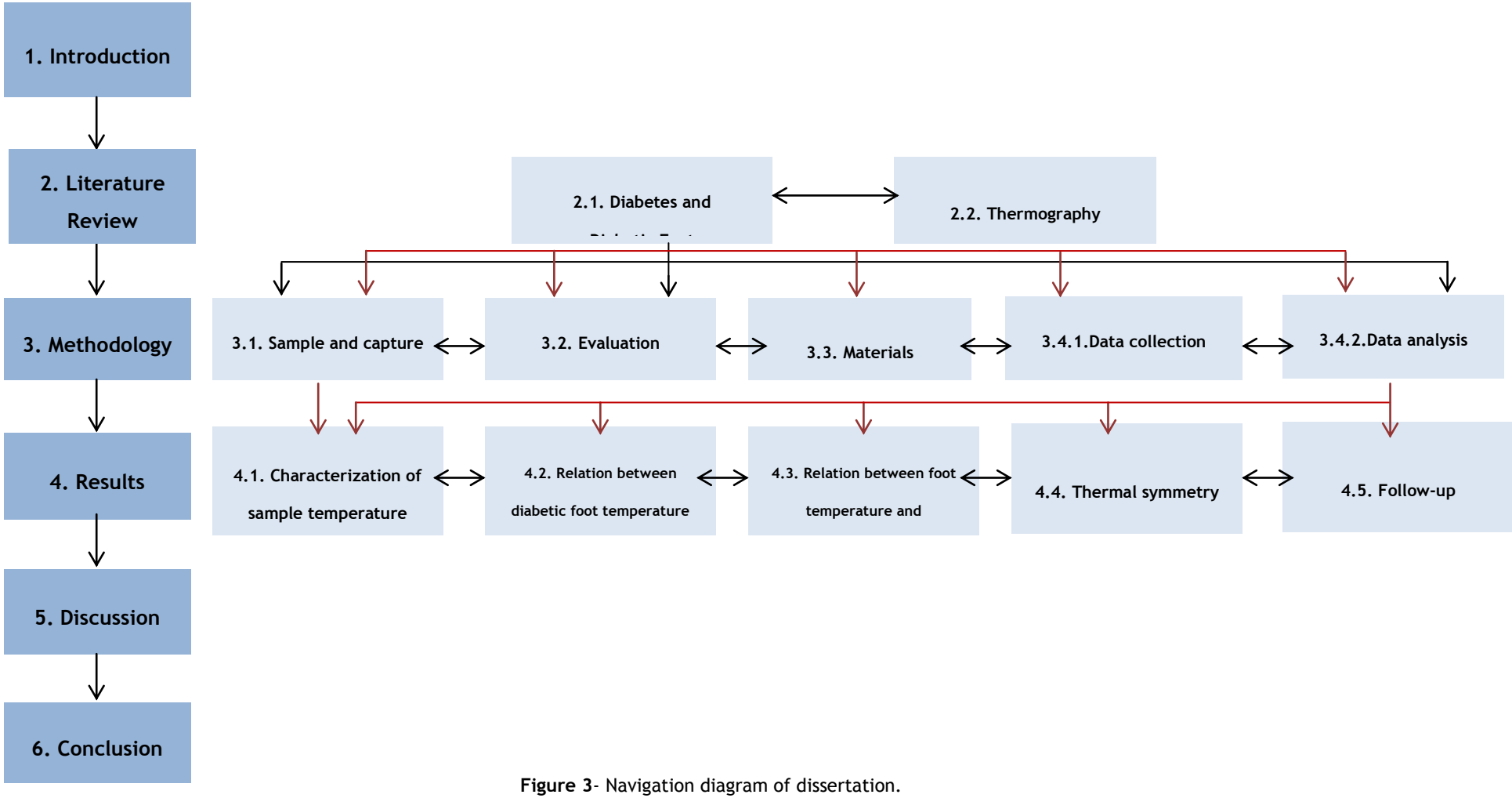


Figure 3- Navigation diagram of dissertation.

Chapter 2

Literature Review

In this chapter, the diabetic foot condition is described and characterized.

Thermography, thermal transfer mechanisms are presented. The role of thermoregulation in the human body, microcirculation and thermal imaging. The past studies of using Thermology in the diabetic foot condition are also outlined.

2.1. Diabetes and Diabetic Foot

2.1.1. Definition and classification of diabetes

D*iabetes mellitus* is a set of metabolic diseases characterized by hyperglycemia, which results from defective insulin secretion, a flawed insulin action, or both. Chronic hyperglycemia is associated with long term damage, dysfunction and failure of several organs, namely the eyes, kidneys, nerves, heart and blood vessels. Several pathogenic processes are involved in the development of diabetes. These range from the autoimmune destruction of pancreatic ß-cells, with consequent insulin deficiency, to abnormalities, which result in insulin resistance [12].

Long term diabetes complications include retinopathy with potential loss of sight, nephropathy, which leads to kidney failure, peripheral neuropathy leading to potential feet ulcers, amputations and autonomic neuropathy which leads to gastrointestinal, genitourinary

and cardiovascular problems, and sexual dysfunction. Diabetic patients are prone to other serious illnesses, since they have a high incidence of atherosclerotic peripheral vascular disease, cerebral vascular disease, hypertension and an abnormal lipoprotein metabolism.

Regardless of what causes it, diabetes is associated with a common hormonal defect, i.e., insulin deficiency, which can be absolute or relative, according to one's insulin resistance. Insufficient insulin has a vital role in metabolic changes associated to diabetes. Hyperglycemia, in its turn, plays an important role in disease-related complications [13].

Diabetes can be classified according to the following categories:

- **Type 1 diabetes:** This type of diabetes accommodates around 5-10% of all diabetics, and is a consequence of the cell-mediated destruction of pancreatic ß-cells, which leads to absolute insulin deficiency. The destruction of these cells happens due to various genetic predispositions and it is also associated to environmental factors, which have not yet been completely defined [12, 13].

- **Type 2 diabetes:** Has around 90-95% of all diabetic population, and is characterized by insulin resistance and relative insulin deficiency. Most of the patients with this condition do not need insulin admission. This type of diabetes frequently remains undiagnosed for years, as hyperglycemia develops gradually and the patient does to notice any of the usual diabetes symptoms. However, these patients face an increased risk of microvascular and macrovascular complications [12].

- **Gestational diabetes:** For many years, it was characterized as any degree of glucose intolerance, which started or was first discovered during pregnancy. Even though, most cases can be managed with medication, this definition is applied depending on whether the condition persisted after pregnancy and does not exclude the possibility that the unrecognized glucose intolerance may have started before or at the same time as the pregnancy [12].

During pregnancy, gestational diabetes requires treatment to optimize maternal blood glucose levels to lessen the risk of complications in the infant. The gestation period is relatively brief for developing serious complications that cause the appearance of ulcers on the feet. However, women who have had gestational diabetes are more prone to develop diabetes in the next 10–20 years [14].

- **Other specific types:** Various types of diabetes are associated with monogenetic defects in ß-cell function. These forms of diabetes are frequently characterized by hyperglycemia at an early age (usually before 25), diminished insulin secretion with little or even no effect in insulin action and have an autosomal dominant inheritance pattern. The

most common form is associated with chromosome 12 mutations in the hepatic transcription factor referred to as a hepatocyte nuclear factor (HNF)-1a. The second type is associated with mutations in the glucokinase gene in chromosome 7p. The least common types result from transcription-factor mutations, such as HNF-4a, HNF-1b, insulin promoter factor (IPF)-1, and NeuroD1. This condition is very rare and was not found information that relates this type of diabetes with diabetic foot.

Diabetes is one of the most common chronic diseases in every country, and its numbers continue to increase in size and in importance. This exponential growth has to do with an economic and urban development, which leads to lifestyle changes characterized by reduced physical activity, increased obesity and an uncontrolled diet [15].

Along with these factors, the *International Diabetes Federation* estimates that this number will continue to grow worldwide, due to population aging and growth and the high prevalence of obesity and a sedentary lifestyle, reaching 522 million people in 2030 [16]. As such, diabetes is considered a serious public health problem, due to being a chronic illness and affects a large population [17].

2.1.2. Definition of diabetic foot

Diabetic foot is the most common chronic complication in diabetic patients. It affects more the patients with type 2 diabetes [18], which has a relation with the duration and success of diabetes treatment. Based on epidemiological studies, it is estimated that 25% of all diabetics will develop serious health problems related to diabetic foot during their lifetime, whilst 5% to 15% of all patients will have their foot or leg amputated [19].

The diabetic foot is characterized through foot lesions as a result of peripheral and/or neurologic vascular changes singular to diabetes, known as the triad: neuropathy, peripheral vascular disease and infection. If this deterioration is not detected at an early stage, it can evolve into gangrene or consequently to limb amputation [20].

Neuropathy causes loss of sensitivity and pain, which contributes to the existence of trauma and ulcerations. The appearance of infection and insufficient irrigation of the lower limbs leads to the progression of gangrene. The diabetic patient most of the times does not realize there is a lesion until the latter, where it is already in an advanced state, which makes treatment more difficult and contributes to the high incidence of amputations in these patients [21].

The important risk factors include: age, type and time of diagnosis, inadequate glycemia control, smoking, alcoholism, obesity, hypertension and lack of hygiene when it comes to footcare. Healthcare professionals to assess diabetics' feet regularly, in order to early identify the risk factors are very important. That can also be changed through promoting self-

care, along with a proper metabolic control, which will, in turn, reduce the risk of ulceration and amputation [21].

2.1.3. Epidemiology

The "diabetic foot syndrome" encompasses a considerable number of pathological conditions, including neuropathy, ischaemia, Charcot's neuroarthropathy, foot ulceration, osteomyelitis and amputation [22].

Patients with diabetic foot injuries frequently present various diabetes-associated complications. As such, there is a need for a multidisciplinary approach, with several specialties involved, such as an endocrinologist, a specialized nurse, a podiatrist, a vascular surgeon, an orthopedist, a physiatrist and a general practitioner [23].

From the pathological conditions present, foot ulcers and amputations are both the most common and the most serious complications and are responsible for a significant mortality. Foot ulcers precede around 85% of amputations, wich can led to the assumption that a success in early detection or adequate treatment of those ulcerations would result in reducing the number of amputations [23].

The risk of a diabetic patient developing a foot ulcer during their life is around 25% [24]. Foot injuries in these patients are the main cause of hospital admission when compared to any other long-term diabetes complication, and they also result in an increased morbidity and mortality. These lesions occur due to the presence of sensory-motor neuropathy and vascular disease [24].

Regarding the etiology of foot ulcerations, about 45-60% of ulcers are purely neuropathic, about 10% are purely ischemic and 25-45% are mixed (neuroischemic) [25] and happen particularly on the sole of the foot in areas subject to high pressure when walking [18].

Besides causing pain and morbidity, the diabetic foot has severe economic consequences. Costs are reduced by foot ulcer prevention interventions, through strategies that promote healing (which shorten the healing period and prevent amputations) [23].

2.1.4. Pathophysiology

Having knowledge of the pathophysiology of the ulceration is essential to provide optimal healthcare, since changing the factors that lead to its development allows better healing the foot or helps keeping it intact, providing to the patient a completely normal life.

There is estimation that 15% of all diabetic patients will have a foot ulcer at some point in their lives, and about 2 to 3% of all diabetics will develop them every year. Many of these ulcers will require prolonged hospitalization to treat subsequent complications, such as infection or gangrene. [26-28].

As Figure 4 shows the relation between the most important factors that lead to a vulnerable high risk of diabetic foot and contribute to the appearance of an ulcera, which are: neuropathy, macroangiopathy, medial artery calcification or Mönckeberg arteriosclerosis and diabetic microangiopathy. When one or more of these factors is present, the existence of a triggering factor which acts on the vulnerable foot will lead to the formation of an ulcer or necrosis [26-28].

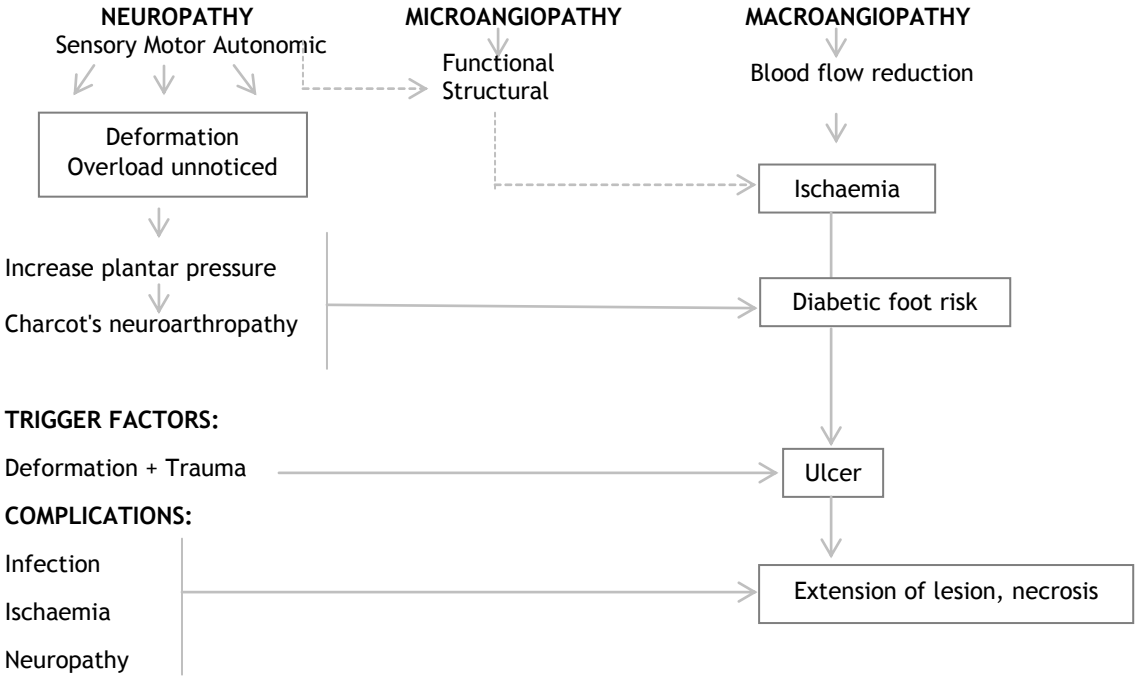


Figure 4- Mechanism of appearance of the ulcer [27].

2.1.4.1. Neuropathy and peripheral vascular disease

Since neuropathy and peripheral vascular disease are the etiological factors most related to the appearance of foot ulcers, it is necessary to understand these two causal mechanisms.

Peripheral polyneuropathy (sensory, motor and autonomic) derives from axon terminal degeneration, where the intensity varies proportional with the size. Since the largest size exists in both inferior limbs, neuropathy is a bilateral complication [23].

Diabetic distal neuropathy can affect the three components of the nervous system: sensory, motor or autonomic, and all of them contribute to the development of foot ulcers. Consequently, somatic (sensory-motor) and autonomic fibers are also affected. The smallest nervous fibers do suffer changes, which causes the loss of pain and temperature sensations.

Subsequently, the largest nervous fibers will also be affected, which will leads to a decreased superficial sensation perception [26].

Neuropathy can have two different classifications:

- **Sensory-motor neuropathy,** consists of a gradual loss of tactile and pain sensitivity, which causes feet to be vulnerable to trauma, called "loss of protective feeling" [28]. The latter is subdivided in two classes: acute sensory neuropathy, which is rare and follows periods of inadequate control or sudden change in metabolic control, and chronic sensory-motor neuropathy, which is the most common type of neuropathy. Instability and loss of balance have been increasingly recognized as possible manifestations of peripheral chronic polyneuropathy, secondary to proprioceptive disturbances and possibly abnormalities in sensitive muscle function. This instability may result in repeated minor traumas or falls and late complications, such as Charcot's neuroarthropathy, which consists of consequential repeated traumas in the foot. These changes are also clearly related to the appearance of ulcers [26].

About 50% of all patients present symptoms, such as: pain, dysesthesia, paresthesia, very warm skin and numbness. However, since about half the patients can be asymptomatic, it can only be diagnosed during a medical exam or when the patient presents a painless foot ulcer [29].

This loss of sensitivity is very serious and may lead to major injuries since, for example, a diabetic person with loss of protective feeling may no longer feel the discomfort of the repeated pressure of a tight shoe or the pain of a pointy or sharp object on the floor. It also leads to foot intrinsic muscle atrophy, causing an imbalance between flexor and extensor muscles, triggering osteoarticular deformities. The latter will change the pressure points in the sole of the foot, leading to overburdening and to a skin reaction with local hyperkeratosis (callus), which, with continuous walking, will evolve into ulceration [28].

- **Autonomic neuropathy**, in turn, consists of an autonomic nervous system injury, namely of the sympathetic nerves, leading to loss of vascular tonus[1], causing vasodilation with an increase in arteriovenous communication and, as a consequence, the direct passage of blood from the arterial to the venous network, decreasing tissue nutrition. This phenomenon leads to hypohidrosis, a skin illness that causes reduction or absence of sweat secretion due to the low activity of the sympathetic system, which causes the dry skin, culminating in the appearance of fissures and changes in the growth and matrix of nails, which much like chronic ulcers, are important entrance points for infections [28,29].

[1] **Vascular tonus** is the degree of sustained constriction of the vascular system, which regulates the peripheral vascular resistance and contributes to the charge against which the heart must pump (Post-Charge) [30].

Vascular disease is responsible for more than 70% of deaths of patients with type 2 Diabetes [29]. Diabetic peripheral vascular affection is divided in microangiopathy, Mönckeberg arteriosclerosis and macroangiopathy caused by atherosclerosis.

Diabetes is associated with an increased risk of peripheral vascular disease. However, this is not frequently the primary etiology of diabetic foot problems, such as ulceration or amputation. It is, nevertheless, implied in the altered response to infections and in the healing process, being present in almost 50% of all amputated patients [26, 29].

This pathogenic entity is, therefore, more important in the persistence and evolution of diabetic foot ulcers then in its appearance. Foot infection and/or ulceration entail the need to increase blood supply to damaged tissue. If the patient has peripheral vascular disease, it may not be possible to answer that need (whether due to ischaemia or because vessels are unable to dilate), causing more tissue damage and causing the infection progression [26].

Given this, its presence worsens the prognosis for these patients, increasing the risk of amputation. Thus, it is of vital importance to identify and treat the co-existing peripheral vascular disease. Vascular disease is frequent in diabetics, but it is only threatening to the limb if there is a skin lesion. Adequate tissue perfusion is vital for the ulcers to heal correctly. Whenever an ulcer does not heal there is a suspicion of arterial failure, which can cause more severe complications [26, 31].

2.1.5. Innervation and vascularization of foot

Diabetic foot is the set of neurological and vascular conditions affecting the feet of patients with diabetes, like aforementioned. So it is important understanding the role of autonomous nervous system and the microvascular system on the overall risk of ulceration in diabetic patients.

Pathological changes in the feet can occur in the muscles (muscles, tendons or ligaments), bone or vascular (veins, arteries, vessels and microvessels). Vascularization region of the ankles and feet are usually more susceptible to such changes given its complexity. Thus, conditions that affect the circulation area, such as diabetes, tend to slow down the blood return, which ultimately lead to swollen feet, pain and accumulation of toxins in the region, in addition to the propensity to wounds and delayed cell regeneration [32].

The innervation of the foot (**figure 5A**) is provided by the following nerves: superiorly by the deep and superficial peroneal nerves; Inferiorly by the medial and lateral plantar nerves; Medially by the saphenous nerve, which extends distally to the head of the 1st metatarsal; Laterally by the sural nerve, including the heel part, and this by calcaneal branches of the tibial and sural nerves [33].

The different zones shown in the figure are also referred to dermatomes, which are areas of the skin that are innervated by nerve fibers that originate from a single dorsal nerve ganglion. Each dermatome is named according to the spinal nerve that innervates it. Correspondence between the skin and the nervous system dermatome is used to help locate the degree of neurological deficit [34].

Foot vascularization (**figure 5B**) is carried out by the following metatarsal arteries distally to the crevices of the fingers, being united with the plantar arch, and plantar metatarsal arteries perforating branches; Arcuate artery that is disposed laterally through the bases of the four lateral metatarsal passing deep to the tendons of the extensor muscles, thus achieving the lateral aspect of the forefoot; Medial artery of the foot corresponding to continuation of anterior tibial artery, and a major source of blood supply to the front part of the foot; Lateral tarsal artery, a branch of the dorsal artery of the foot laterally and follows a curved path under the short extender fingers with the aim of supplying this muscle and tarsal joints and the underlying [34].

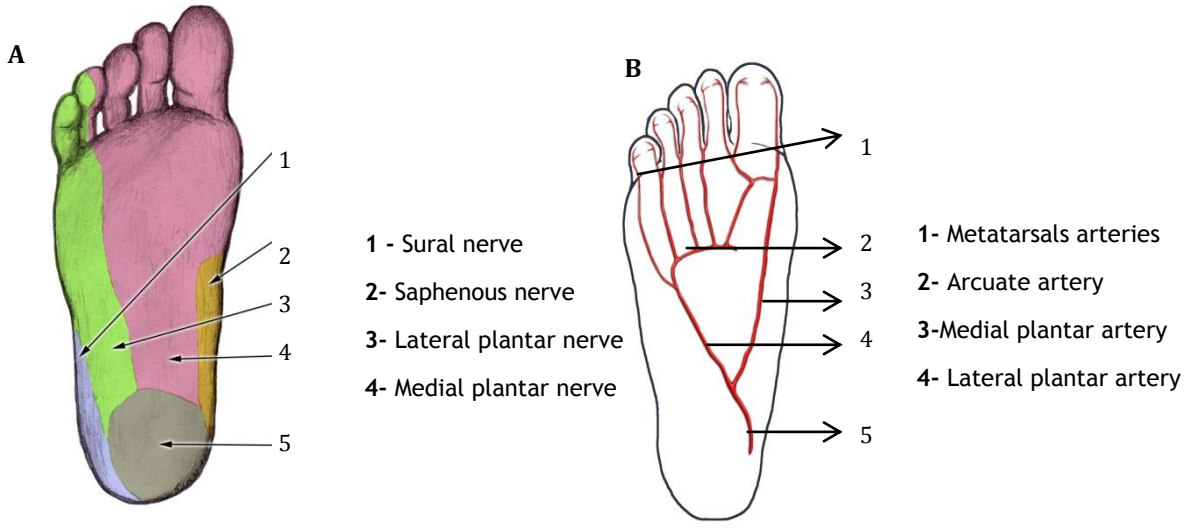


Figure 5 - Location of plantar nerves (A) [35]; Location of plantar arteries (B)[36].

2.1.6. Diagnosis

As previously mentioned, the ulceration of the diabetic foot is associated with peripheral vascular disease and peripheral neuropathy, which are frequently combined. However, individuals who have a high ulceration risk can be easily identified through a careful foot examination. Education and periodical follow-ups are also indicated in these cases [23].

When it comes to the physical examination, the *American Diabetes Association* (ADA) approves a few different tests to identify sensory loss in the sole of the foot due to neuropathy. These tests are:

a) Semmes Weinstein monofilament test, illustrated in Figure 6, in which the incapacity to feel the necessary pressure to bend the 10g monofilament when tested in various areas of the foot is compatible with sensory neuropathy [37].

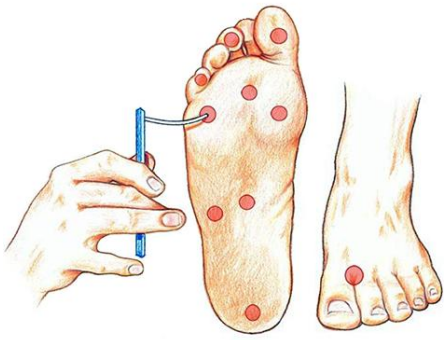


Figure 6 - Evaluation of the diabetic foot using the Semmes Weinstein [37].

b) Reflex hammer test. Deep sensation can be assessed through the Achilles tendon reflex test by using the reflex hammer, and absence of reflex is connected to an increased ulceration risk.

c) Testing with a 128 Hz tuning fork and with a biothesiometer, by which we can assess vibration perception. An abnormal response can be defined when the patient loses vibration perception, but the latter is still detected by the examiner [37, 23].

All these tests are used to determine the risk of ulceration but the monofilament test, due to its simplicity and low cost, is considered to be the best choice [37].

To assess peripheral vascular disease, palpation of pedis and posterior tibial arterial pulses is recommended, characterizing them as present or absent. For patients with signs and symptoms of vascular disease or an absent pulse, an ankle-brachial index (ABI) measurement must be performed, and a vascular surgeon referral must be considered.

ABI is an accurate way of assessing arterial perfusion, where you can check systolic arterial blood pressure in the leg (posterior tibial pulse) and in the arm, measuring the ratio between them. While the patient is resting, an index is considered normal when below a rate of 0.9 to 1.3. A decreased index suggests a vascular disease, considered light to moderate when the index is 0.4 to 0.9 and serious when below 0.4 [37].

Some clinical features that distinguish the type of foot ulcers are summarized in Table 1.

Table 1- Clinical features that distinguish neuropathic and vascular foot ulcers [38].

Neuropathic ulcers	Vascular ulcers
Painless	Painful
Located at points of high pressure	Often located at the extremities
Warm foot	Cool ischaemic foot
Bounding foot pulses	Absent foot pulses

These methods are used daily in the care of patients with diabetic foot, however can be a little subjective. Depend on the person who executes them, and can be lengthy. Thus arises the need to implement new methods of detection and monitoring diabetic foot more efficient and objectives, as for example the thermography.

2.1.7. Prevention

The best form of prevention is, unquestionably, health education. Diabetics must be advised to reduce risk factors, such as smoking, reducing fat intake, stabilizing or reducing weight and having an optimal glycemia control, among others [39].

Diagnostic exams must be performed at least once a year, and healthcare professionals must educate patients about self-monitoring, i.e., the daily inspection of their feet, since the absence of symptoms does not mean that their feet are healthy. During this inspection, it is advisable to pay special attention to color, temperature, joint mobility and nail problems.

Since footwear is one of the main causes of ulceration, patients should not wear shoes that are too tight or too loose, and they should be inspected beforehand. Pathologies associated with calluses, nails and skin must be treated regularly. It is also highly recommended to maintain good foot hygiene and to use moisturizes to avoid the appearance of fissures [40].

Consequently, the best way to prevent diabetic foot complications is to educate the patients, so that they can check their feet every day and consult a professional whenever any anomality is present. This will ensure an early diagnosis and an effective treatment [39, 40].

2.2. Thermography

2.2.1.Thermology: principles and procedures

Thermology is the field of Physics that studies heat, and the manifestations of the types of energy, which produce temperature variations (heating, cooling, or even the change in physical state that derives from these two variations) [41].

Thermology studies the way by which heat can be exchanged between bodies, as well as the characteristics of each heat transfer process, which consist of four different mechanisms: conduction, convection, evaporation and radiation [41].

In order to understand the role of thermology, it is firstly necessary to distinguish between temperature and heat. Heat is tangible and consists on thermal energy in motion, i.e., it is energy that is in constant motion, always being transferred from one hotter body to a cooler one. Temperature, on the other hand, is a measure of the status of molecule agitation. The temperature is proportionally related with the molecules agitation [41,42].

Medical thermography consists on documenting the distribution of thermal radiation emitted at the surface of the skin, by using infrared imaging. Both the skin's galvanic impedance and the vasomotor and sudomotor responses can be assessed by studying the way skin responds in medical infrared images, i.e. through infrared thermography. This technique involves no contact and no form of energy is transmitted to the body, which makes it a complementary diagnostic and treatment-assessing test with great potential [43].

There are four mechanisms of heat loss: conduction, convection, evaporation and radiation.

- **Conduction** is the transfer of heat from one solid object to another when in direct contact with it [53].

- **Convection** is based on heat transfer by the movement of a fluid (liquid or gaseous) in the body. Blood, heated by the visceral and the somatic metabolism, is convected by the vascular system and transferred to the inside of the body, and then to low temperature areas, thus representing the largest heat transfer mechanism inside the body.

- **Evaporation** is the conversion of water into vapor, by means of thermal energy. This process occurs throughout the surface of the body, and mainly in the respiratory system. This mechanism is of very little importance in the thermal image when the individual is in balance with his environment [53].

- **Radiation** represents the largest heat loss mechanism in the human body, responsible for 60% of its total loss. Thermal energy is converted into electromagnetic radiant energy, which is emitted by the body in the infrared spectrum band. Central blood temperature is brought to the skin's vascular network, where thermal energy is converted into radiant energy and transmitted to the environment. This radiation is detected through infrared cameras [45,53].

2.2.2. Thermography and its application

The biomedical use for thermography has increased over the last fifty years. Since this is a completely non-invasive technique, its use has been helpful in terms of medical research as a sensitive complimentary diagnosis method for different clinical and experimental levels [44].

Thermography offers valuable information on the temperature differences of different parts of the human body surfaces. It enables to monitor the nervous system, metabolic or vascular disturbances, skin cancer, pain syndromes, soft tissue damage, virus infections and others by comparing thermal changes and differences. Since infection and inflammation can appear in any part of the human body, causing temperature changes, thermography is therefore a valuable tool for repetitive monitoring which will not harm the patients.

Since the camera used for temperature detection only receives natural thermal energy emitted by the body, and no harmful energy is used, this technique can be used continuously in various tests over time [44, 45].

2.2.3. Thermoregulation and heat transfer mechanisms

Clinical information obtained by thermography is not directly based on changes in metabolic activity and heat production. It is based on heat distribution in the body and the regulation of that heat loss, especially at the surface of the skin. Metabolic heat is brought from the inside of the body, by the vena cava and the larger veins where it is mixed and distributed by the aorta and its branches [46].

The human body has a good homeostatic control mechanism for body conditions, including temperature, pH and others. Temperature is a useful parameter to assess the body health condition. The core temperature of our body is usually kept at 36.8 ± 0.6°C and, if the temperature in a certain area is higher or lower, and therefore not normal, it becomes an indicator of a possible problem, such as infection or necrosis [47].

The skin works as an interface between body and environment. It is possible to measure the temperature along the surface of the skin. The balance between the body and surrounding environment made through thermoregulation. Blood flow play an important role in this process, any changes in it induces changes in skin temperature [48].

Human skin blood flow responses to body heating and cooling are essential to the normal processes of physiological thermoregulation. In humans, reflex sympathetic innervation of the cutaneous circulation has two branches: a sympathetic noradrenergic vasoconstrictor system, and a non-noradrenergic active vasodilator system. Noradrenergic vasoconstrictor nerves are tonically active in normothermic environments and increase their activity during cold exposure, releasing both norepinephrine and cotransmitters (including neuropeptide Y) to decrease skin blood flow. The active vasodilator system in human skin does not exhibit resting tone and is only activated during increases in body temperature, such as those brought about by heat exposure or exercise [49].

Figure 7 illustrates the vasodilation and vasoconstricition processes. In vasodilation, the hypothalamus sends nerve impulses via parasympathetic nervous system to blood vessels near

the skin. Smooth muscle in vessel walls relaxes, but 'shunt vessel' constricts so more blood goes to the surface. In vasoconstriction the sympathetic nerve impulses to blood vessels near the skin. Smooth muscle in vessel wall contracts so less blood flow, shunt vessel relaxes so less blood flows to the surface capillaries. Less heat lost by radiation is thus typical of vasoconstriction [50].

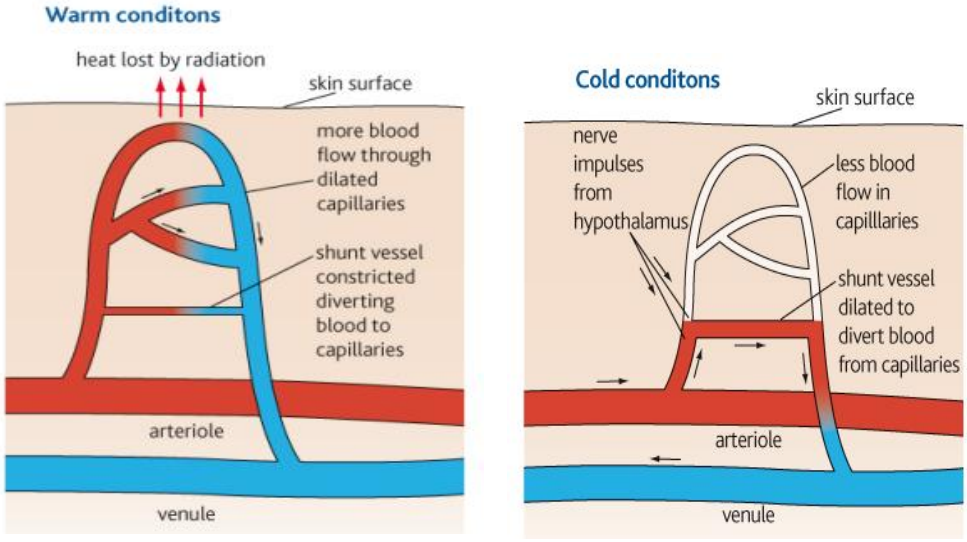


Figure 7- Illustration of vasodilation and vasoconstriction processes, respectively **[50].**

There are other mechanisms that help maintain body temperature, sudoresis and muscle contraction. The sudoresis, which is the act of producing and releasing sweat, begins when the core body temperature is above 37°C. This mechanism is regulated via stimulation of the sweat glands by cholinergic sympathetic nerves and sometimes in situations such as exercise or stress by high concentrations of epinephrine and norepinephrine [51].

Muscle contraction is also an important source of thermal energy - muscle thermogenesis. This can be stimulated by the cerebral cortex or involuntarily by the hypothalamus. The posterior hypothalamus modulates the degree of inhibition of the activity of neurons in the spinal cord.

The decrease of inhibition of the previous neurons (promoted by a decrease in core body temperature below the set value) at an early stage leads to increased muscle tone, and subsequently repetitive contractions occur.

The rapid involuntary skeletal muscle contraction may result in a 4-fold increase in heat production, of 2 times the oxygen uptake and the 6 times the metabolic rate [51].

Thus, the thermoregulatory control of human skin blood flow is vital to the maintenance of normal body temperatures during challenges to thermal homeostasis.

Skin temperature in a given area depends on that area's blood supply and on the thermal conductivity of subcutaneous structures. Cutaneous microcirculation is mainly controlled by sympathetic activity and is, for that reason, frequently used experimentally as a measure of

sympathetic activity, since arterioles, particularly the ones in the skin and fingertips, only have sympathetic adrenergic constrictor nerves [52]. The peripheral and central nervous system (CNS) receptors detect minimal thermal variations and change the peripheral blood flow in order to maintain a constant central temperature, adjusting the vascular network in dissipating the excess heat at the surface of the skin. It is the distribution of blood in that superficial vascular network that is observed by thermography [54].

Thermography is an imaging technique that maps the distribution of body surface thermal radiation into images, providing a real-time microcirculatory and autonomous nervous dynamic physiological assessment of cutaneous surface. Thermography allows quantitative and qualitative mapping of superficial temperature, which can be related to different pathological conditions and blood flow [53].

2.2.4.Infrared radiation and thermography

Electromagnetic radiation is continuously emitted from all substances because of the molecular and atomic agitation associated in their internal energy. In equilibrium, the internal energy is associated to the temperature. An object can be characterized by its capacity of absorbing or emitting electromagnetic radiation.

Electromagnetic radiation can be classified according to its wavelength and frequency [55]. The electromagnetic spectrum includes gamma rays, X-rays, ultraviolet, visible, infrared, microwaves, and radio waves. The difference between these different types of radiation is their wavelength and frequency. Wavelength increases, and frequency (as well as energy and temperature) decreases from gamma rays to radio waves [55].

Infrared waves have wavelengths longer than visible and shorter than microwaves, and have frequencies lower than visible and higher than microwaves.

Infrared radiation (IR) encompasses wavelengths that go from 0.76 to 1000 μm, divided into short, medium and long wave, as illustrated in Figure 8.

Human body emissions, which are usually measured for diagnostic purposes, take up a narrow band of wavelengths that go from 8 to 13.5 μm, with this area being mentioned as the long wave infrared [56].

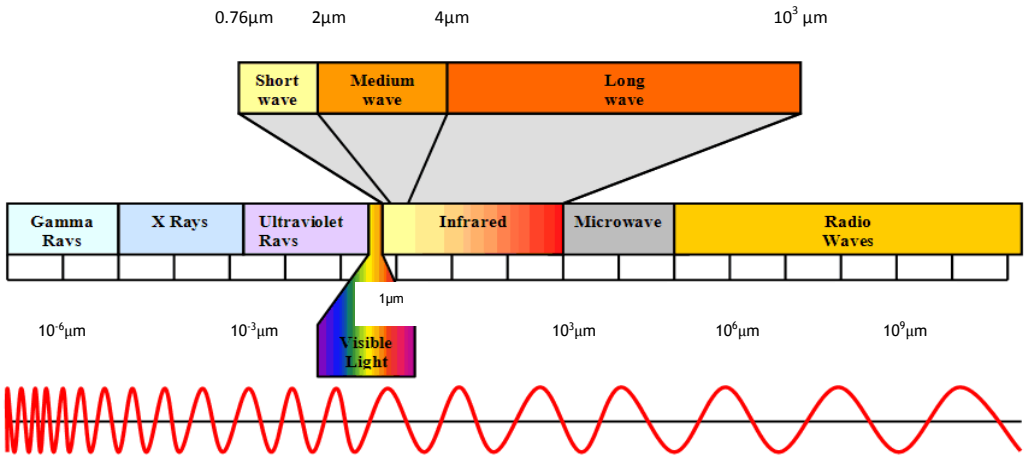


Figure 8- Wavelength of infrared radiation, divided into short, medium and longe waves [57].

Computerized infrared thermography is a method that allows for the viewing, documentation and measurement of infrared rays along the human body. According to Stefan-Boltzmann, this emission is proportional to the temperature of the skin and is directly related to the blood flow inside the blood vessels [58]. The Stefan-Boltzman law of radiation states that the radiant output increases to the fourth power of its temperature. The conduction and convection components increase only in direct proportion with the temperature change. In other words, as the temperature of a heat source is increased, a much greater percentage of the total energy output is converted into radiant [59].

Thermograms are IR-generated images, and are used for medical diagnostic purposes based on the fact that many pathological processes in the human organs manifest themselves as local changes in heat production, as well as changes to the blood flow pattern of affected tissues [58]. Modern infrared technology has opened new perspectives, especially when it comes to the use of thermal images to map the temperature of the surface of the body with a remote sensing camera, which allows for a quick and effective complimentary diagnostic and treatment assessment information [44].

2.2.5. Previous Studies

Infrared thermal imaging of the skin has been used for about five decades to monitor the temperature distribution of human skin [45]. The human body is an efficient thermal system, and we are entirely dependent on the ability of the body to self-regulate human body temperature.

Since diabetes is a disease with high prevalence worldwide, in the last decades many studies have been developed, and researches showed that there is a relationship between increased skin temperature and foot complications in diabetes. It also contributed for a greater understanding of termal physiology and the relationship between skin temperature and blood perfusion [60].

Abnormalities such as malignancies, inflammation, and infection cause localized increases in temperature which shown as hot spots or asymmetrical patterns in a thermogram. Therefore thermography is a powerful detector of the location of problems that affect a patient's physiology [45].

One of the first studies in this area was in 1967, in which Brånemark [61] compared feet of 16 diabetes patients with and without manifest vascular complications using infrared thermography. This technique revealed that all 16 diabetics had abnormalities in the emission patterns from feet, and he concluded that thermography was a useful technique for the study of circulation and metabolism in diabetes.

Lavery et al. [62] performed a long study in which 173 individuals with a previous history of diabetic foot ulceration participated. The main goal was to evaluate the effectiveness of a temperature monitoring instrument to reduce the incidence of foot ulcers in patients with diabetes who have a high risk for lower extremity complications.

All the participants all were instructed to self-monitor their feet by measuring temperatures using a thermometer and register all the values. The feet was divided in different regions of interest (hallux; first, third, and fifth metatarsal heads; midfoot; and heel), and if they verified a difference of temperature of 2.2°C they should call a nurse. The results shown that over 50% of patients did call the nurse, and 8% of them went on to develop ulcers. Thus concluding that if patients are instructed to monitor their feet at home, they may simply prevent serious conditions such as the appearance of ulcers that can result in amputation later.

Armstrong et al. [63], made a similar approach that have the purpose of evaluate the effectiveness of home temperature monitoring to reduce the incidence of foot ulcers in high-risk patients with diabetes. This study involved 225 participants with diabetes at high risk of develop ulcers and they were instructed to inspect their feet daily and measure the temperatures of six regions and record their findings. If patients verified a temperature difference higher than 2.2°C, they should contact the study coordinator.

The results of this study has shown that 8.4% ulcerated over the study period. Those patients who ulcerated had a temperature difference that was 4.8 times greater at the local of ulceration in the week before the ulcers appeared there did a random seven-consecutive-day sample of 50 other subjects who did not ulcerate.

Once again, this study showed that the temperature is an indicator of possible foot problems and that self-monitoring, after the individuals are trained to take care of your feet,

is a good way to keep a tighter surveillance for possible development of ulcers in the diabetic foot.

In 2008, "The Glamorgan Protocol" [64] was defined, which is a project that is based on the creation of an atlas of the normal distribution of skin temperature, in order to fill gaps in knowledge of the distribution of skin temperature in healthy subjects. This atlas is a set of views of body positions and regions of interest of normal infrared images of healthy subjects, and when this protocol is strictly applied for image recording and evaluation, increases the reproducibilty of findings from thermal images.

The guideline [64] defined 24 body positions and 90 regions of interest in order to construct a clinical database of reference thermograms. The improved reproducibility of body positions and location of regions of interest has been shown to have a marked influence on both the accuracy and precision of temperature measurements obtained from thermal images [65].

The assessment and posterior eradication of diabetic foot ulcers is a complex and challenging process. The underlying pathophysiology lead to a chronic inflammatory stage, which may prevent appropriate healing, therefore Bharara et al. in 2010 [66], used quantitative thermography to provide a useful numerical índex (WII – Wound Inflammatory Index) to assess wound healing. In this study, the authors propose a new tool for quantifying wound conditions, which includes the thermal features and wound size, both of which may play a key role in determining the duration of would healing. It provided a standardized methodology using thermal imaging for calculating a thermal index (TI) supported with a case report from assessment of a diabetic foot ulcer. Typically, when using infrared thermography, the anatomical surfaces of the foot were examined to identify potential hot/cold areas where inflammation or circulatory increase/loss is occurring, respectively. But, in this case infrared and visible imaging were used to determine the shape, area, curvature, and eccentricity characteristics, showing a new potential of infrared thermography.

In studies related to body temperatures one of the parameters to be considered is the thermal symmetry value of human body. This important fact has been studied and proven by Ring [67] in a study of the lower leg.

Vardasca, et al. [68] based on the standard for recording and evaluation “Glamorgan Protocol” aforementioned, confirmed and defined that the highest thermal symmetry value for the upper and lower extremities was of 0.5±0.3 ºC.

Such as infrared thermal imaging is being increasingly utilized in multiple studies of the body and different medical conditions, the data on the thermal symmetry (or the lack of it) provides valuable information for the health professionals in assessing pathological states.

A computational analysis application [68] was developed to standardise and optimise the time of analysis. This tool performs thermal image morphing based on anatomical landmarks preserving the temperature values associated with the regions of interest (ROI) and generates

statistics about mean temperature, standard deviation of those ROI's. Thermal Symmetry assumptions can therefore be made with higher confidence when assessing abnormalities in specific pathologic states.

Balbinot, et al. [69] evaluated plantar thermography sensitivity and specificity in diagnosing diabetic polyneuropathy using cardiac tests as a reference standard because autonomic small fibers are affected first by this disease. Two thermographic variables were studied: the thermal recovery index and the interdigital anisothermal technique.

The plantar infrared image was recorded at baseline followed by the provocative maneuvers using the cold stress test. After 10 minutes, a new plantar infrared image was recorded to evaluate the thermal recovery index. To calculate the recovery index, the mean temperatures of 10 regions of interest with similar dimensions were used: the hallux, 1st, 3rd, and 5th metatarsal heads and heel on both soles. Balbinot proved that plantar thermography was useful in the early diagnosis of diabetic neuropathy, particularly the small and autonomic fibers that are commonly associated with a sub-clinical condition.

Jaap J. van Netten et. Al [70], have led studies of the diabetic foot using thermography to another level. Although several previous studies have demonstrated how thermography can be useful to detect and monitor diabetic foot complications, however, it still not being used in common medical practice.

The purpose of this research was to explore the first steps in the applicability of high-resolution infrared thermal imaging for noninvasive automated detection of signs of diabetic foot disease. Their main goal is to develop an intelligent telemedicine monitoring system that can be deployed for frequent examination of the patient's feet to timely and automatically detect signs of diabetic foot complications, such as ulcers.

In this study [70] thermal images of 15 participants, divided in 3 groups of 5 people each (diabetic patients without signs of foot complications, patients with local signs of foot complications and patients with diffuse complications) were collected and processed (using Matlab). The results shows that there is no diferences in mean temperature higher than 1.5°C between the ipsilateral and the contralateral foot in the firt group of patients, for the second group the results were similar and for the last group, it was found that mean temperature differences were higher than 3°C.

This is a very recent study [70], but the authors had promising results and showed that it is possible to detect signs of diabetic foot complications with an algorithm based on parameters that can be captured and analyzed with a high-resolution infrared camera.

Peregrina-Barreto et. Al [71], proposed a methodology that obtains quantitative temperature differences in the plantar area of the diabetic foot for detecting ulceration risks. Such methodology is based on the angiosome concept and imaging processing techniques. A methodology was presented aiming at providing quantitative information about abnormal temperature differences in symmetric regions between feet and inside of the same

foot. For this, the plantar area was divided into four main regions (angiosomes) and the temperatures inside those regions were grouped in classes according to a color similitude criterion.

An index (ET) based on the relation between the class with larger area and its adjacent classes was proposed in order to estimate a representative temperature for each angiosome. A second analysis was performed to study the temperatures inside the angiosomes with the aim of detecting the presence of small abnormal areas (hot areas). This estimator was capable to detect the presence of abnormal regions in the initial phase that, for their smaller area, were not detected by the estimator ETD. Through this way, it was possible to analyze the whole plantar area by providing quantitative information to determine the presence of regions in possible risk of ulceration.

In summary, without any doubt, temperature is a crucial parameter for the physiological study of diabetic foot. All this studies proved that thermography has great potential and can bring reliable information to help specialists in early detection of the ulceration risks and to monitor treatments.

Chapter 3

Methodology

In this chapter, the sample characterization, the used materials, the capture protocol and the analysis approach are described.

3.1. Sample and capture images protocol

This empirical study was based on a convenient sample. The sample consisted in 90 participants of two groups of participants: a group of diabetic patients of the Diabetic Foot Clinic at the Hospitalar Center of Porto (CHP) and a control group constituted by healthy volunteers, who did not have diabetes or any other disease or pathological complication.

The criteria for inclusion for this sample were diabetics patients of CHP and healthy participants without diabetes. The criteria for exclusion for healthy participants was having history of any injuries/surgeries in the foot. For diabetic participants were excluded from the study samples individuals with amputated foot regions.

The sample was constituted by men and women without ethnic distinction, aged between 21 and 87 years. Inflammation was provided about the research and volunteers were invited to participate. Their participation in this study was voluntary, and they may quit at any time without prejudice to them.

The total sample consists of healthy individuals and diabetics, who were divided into three groups. The reason for this division is that it is not possible to apply a stimulus across the sample of diabetic patients, due the logistic and short time of medical appointment. Thus the groups that constitute the total sample of 90 people, including healthy and diabetic

individuals to which a stimulus was applied and a third group of diabetic individuals without a a stimulus application.

Before data collection, ethical approval was requested and obtained from the ethics comitte of the CHP (Appendix A), enforcing that all participants were treated fairly and equaly treated and all the available resources were used with responsability.

On the day of the assessment, it was requested from the participant to sign an informed consent form (Appendix B) and to fill in a questionnaire (Appendix C), followed by a period of thermal acclimatization to the examination room and image acquisition. A document with information about thermography procedure was also given to the volunteers (Appendix D). It is noteworthy that this investigation was completetly safe and painless, it did not presented any risk to the individual, and all data collected was confidential.

Figure 9 shows the sample distribution, the total sample consisted of 90 participants, including healthy (with stimulus) elements (N = 40), diabetics (with stimulus) elements (N = 14) and diabetics (without stimulus) elements (N=36).

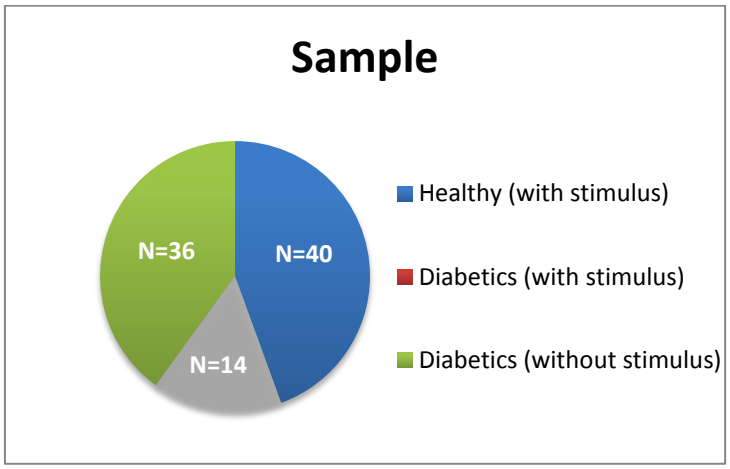


Figure 9- Participants distribution, divided in three groups.

Table 2 shows the distribution of healthy (with stimulus), diabetics (with stimulus) and diabetics (without stimulus) participants by gender.

Table 2- Distribution of participants by gender.

Participants	Female [N]	Male [N]
Healthy (with stimulus)	24	16
Diabetics (with stimulus)	8	6
Diabetics (without stimulus)	13	23

Table 3 shows the distribution of healthy (with stimulus), diabetics (with stimulus) and diabetics (without stimulus) participants by age interval. Healthy participants have ages between 18 and 39, and diabetic participants are a older sample with ages between 18 and ≥70 years.

Table 3- Distribution of participants by interval of age.

Interval of Age (years)	Healthy (with stimulus)	Diabetics (with stimulus)	Diabetics (without stimulus)
18 - 29	39	0	1
30 - 39	1	1	2
40 - 49	0	1	0
50 - 59	0	3	6
60 - 69	0	3	9
≥70	0	6	18

Table 4 shows the distribution of healthy (with stimulus), diabetics (with stimulus) and diabetics (without stimulus) participants by glicemia interval. Both groups of healthy and diabetic participants have a higher frequency in the glicemia interval ≥125 mg/dl.

Table 4- Distribution of participants of interval of glicemia.

Interval of glicemia (mg/dl)	Healthy (with stimulus)	Diabetics (with stimulus)	Diabetics (without stimulus)
<100	11	0	8
100 - 125	4	4	11
≥125	25	10	17

Table 5 shows the distribution of healthy (with stimulus), diabetics (with stimulus) and diabetics (without stimulus) participants by Body Mass Index (BMI) interval. This value was calculated from the values of the weight and height of participants through the equation 1:

$$BMI = \frac{Weight\,(kg)}{Height^2(m)} \quad \text{(Equation 1)}$$

Healthy participants have a BMI between <18.5 and 30, and diabetic participants have a larger range with BMI between 18.5 and ≥35.

Table 5- Distribution of participants by BMI interval.

Interval of BMI (kg/m^2)	Healthy (with stimulus)	Diabetics (with stimulus)	Diabetics (without stimulus)
<18.5	1	0	0
18.5 - 25	32	6	18
25 - 30	7	4	11
30 - 35	0	3	4
≥35	0	1	3

Figures 10 and 11 illustrate the distribution of diabetic participants by diabetes type and ulcer type associated with the diabetic foot, respectively.

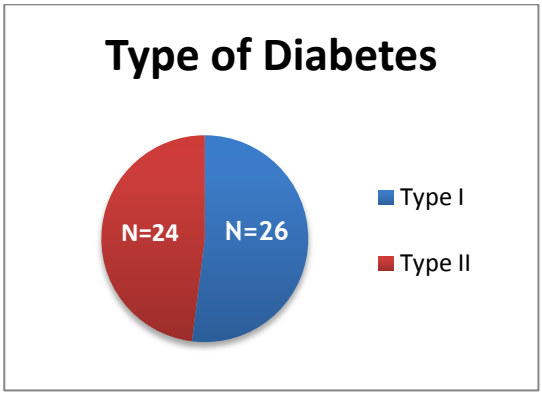


Figure 10- Distribution of diabetic participants by diabetes type.

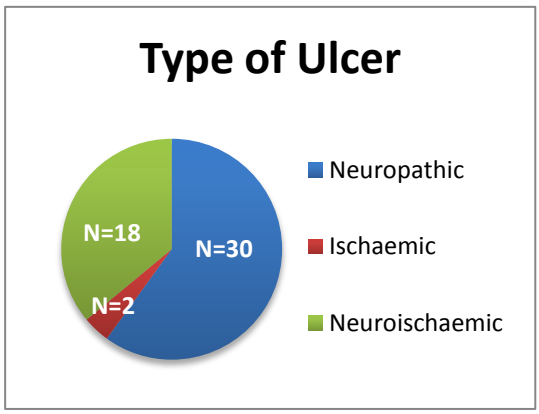


Figure 11- Frequency of diabetic participants by ulcer type.

3.2. Evaluation instruments

3.2.1. FLIR Thermacam Researcher Pro

ThermaCAM Researcher Pro is a robust real-time digital storage, measurement, and analysis software. This tool digitally stores and retrieves static and sequences of infrared images and provides detailed, precision analysis and measurement tools for capturing, recording, and studying extremely high speed thermal events. This was the software used to capture and analyze infrared images throughout this study, and is illustrated in figure 10 [72].

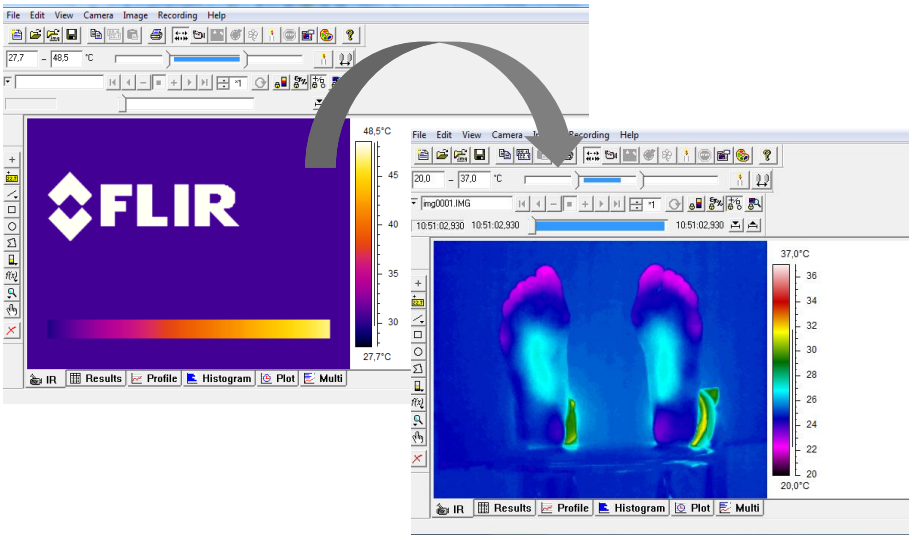


Figure 12- Illustration of ThermaCAM Researcher Pro software for an analysis of foot thermal image.

3.2.2. Blood glucose test

Once this study is related to diabetes, it was important to measure the glycemic index of the volunteers. For such a glucometer was used to measure glicemia, and these values were grouped into three categories: >100 mg/dl, 100-125 mg/dl and ≥125 mg/dl. Blood glucose levels of diabetic individuals were all measured in the fasting state. Glicemia of healthy individuals was not measured in the fasting state due to the different availability of the participants.

3.3. Materials

The equipment used for data collection were:

- FLIR A325 camera, to capture the thermographic images. This thermal camera has an integrated spatial resolution of 320x240 pixels, which has sensors that measures

temperatures ranging from -20°C to +120°C. Its thermal sensitive is of 50mK and has an accuracy ± 2% of the overall reading [73].

- ThermaCAM Researcher Pro 2.10, a Windows-based infrared software package for capturing, recording, and analyzing thermal images.

- Tripod to install and position the camera and the level of patients;

- Fan *Tristar VE-5955 (45W)*, for apply a cold stimulus to the patient;

- Sensor *Testo 175 H1*, for measuring temperature and humidity of the room;

- Glucometer *eBsensor NIST standard SRM965* to measure glucose volunteers (precision of 0.007 mg/g);

- Lancets eBsensor;

- Microsoft Excel 2010, to organize data for subsequent statistical analysis;

- SPSS v21.0 (Statistical Package for the Social Sciences) to statistical processing.

Some of this materials and their position for thermal images capture are illustrated in Figure 13.

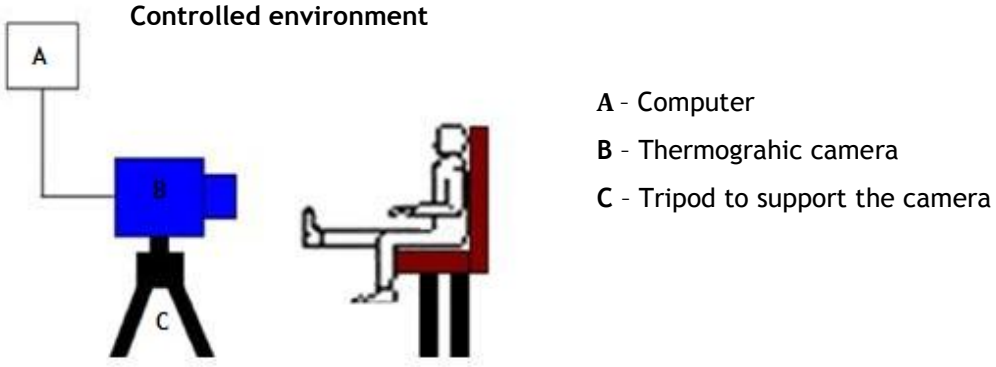


Figure 13- Illustration of equipment for capturing thermographic images. The temperature and humidity of the room should be maintained within comfortable limits, and the camera must be positioned perpendicular to the observation surface at a distance of 80-150 cm from the feet of the volunteer to minimize geometric errors in temperature measurement. [74]

3.4. Procedures

3.4.1. Data collection procedure

Data collection procedure was accomplished according to a thermal protocol (Appendix C). Thermal images were collected in a temperature-controlled room, and the body region being observed, the plantar feet, were bare and free of any metal ornament or other object type, which ensures that the thermal radiation emitted naturally from the human body, is not absorbed or scattered by any of the objects.

To enable the temperature of the individuals remains balanced with the ambient temperature, about 22±1°C it was necessary that before start capturing images of the volunteers, remained in the room for 10 min. So that the body remains at equilibrium with the environment temperature and relative humidity (<50%) and air flow (<5m/s) that have been kept under control.

Thermographic images were captured in three stages:

1) Following the individual to be climatized at room conditions (10min);

2) After application of a cold stimulus (applied by a fan for 2 min);

3) 5 minutes after the capture of the second image.

The plantar foot capturing method is illustrated in Figure 14. In this study a cold stimulus was applied, with the intention of causing an imbalance of temperature in order to measure the response time and maximize physiologic response.

This way the images were captured at 3 different stages to try to understand how physiological processes respond and outlines the temperature profiles of healthy individuals and diabetic individuals within a certain period of time.

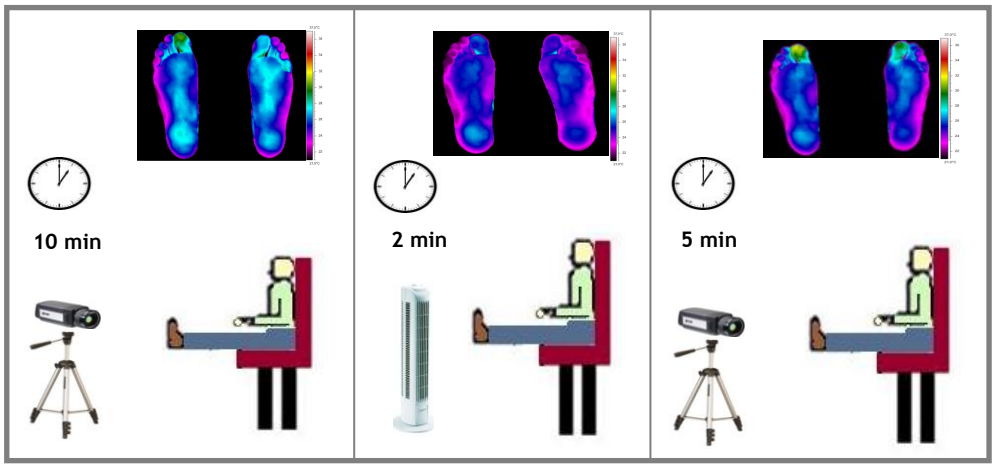


Figure 14-Illustration of thermal imaging over the three stages.

Since the measurement tool used for this study is the temperature of a region of the human body, it was important to record the values of humidity and temperature in the environment were thermal images were collected. The environment that surround us affects our body balance, and therefore these two factors are important to consider.

Table 6 presents the data characterizing the sample relative to the Mean and Standard Deviation of humidity and temperature by study group.

Table 6 - Mean and Standard Deviation of humidity and temperature by Group (Diabetics Vs Healthy).

	Healthy participants	Diabetic participants
Humidity	45.06 (±4.57)	67.87 (±6.28)
Temperature	23.32 (±0.80)	24.97 (±1.41)

3.4.2. Data analysis procedure

3.4.2.1.Selection of Regions of interest (ROIs)

To analyze the temperature of the foot over the 3 stages, it were selected 15 regions of interest on foot (ROIs). This ROIs were based in the anatomy (Section 2.1.5), the ANS are based in the feet dermatomes location and the VS are based in the main perfurated blood vessels location. Images were then analyzed in two ways:

According the autonomic nervous system (ANS) with 6 ROIs (Figure 15), and the vascular system (VS) with 9 ROIs (Figure 16). For all ROIs their absolute mean temperature was measured.

This measurements of ANS and VS ROIs were made with ThermaCAM Researcher Pro software for all participants. Its thermal symmetry for each ROIs was also calculated through the equation 2:

Thermal symmetry = |Temp. Left foot – Temp. Right foot| (Equation 2)

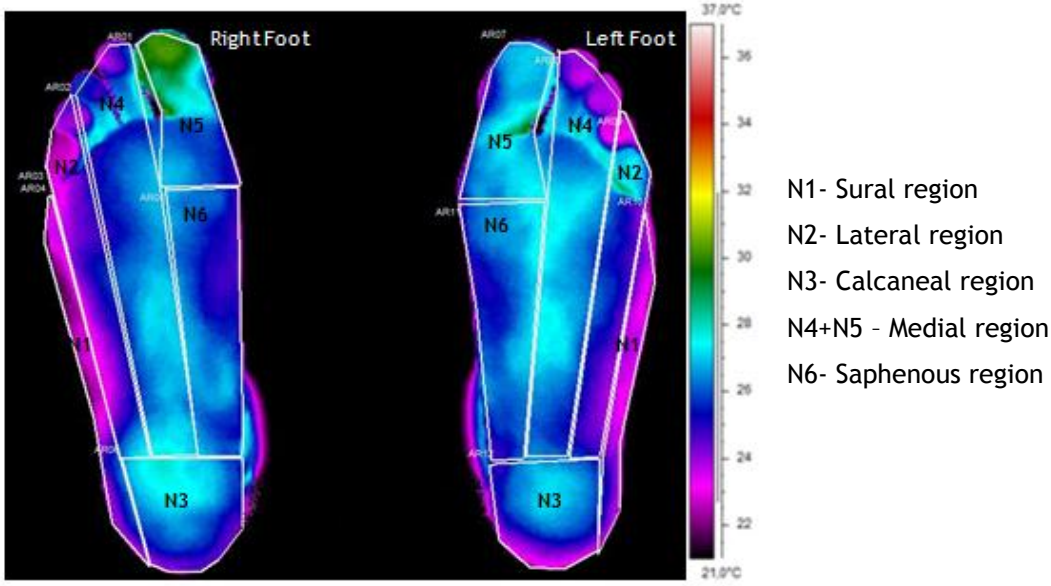
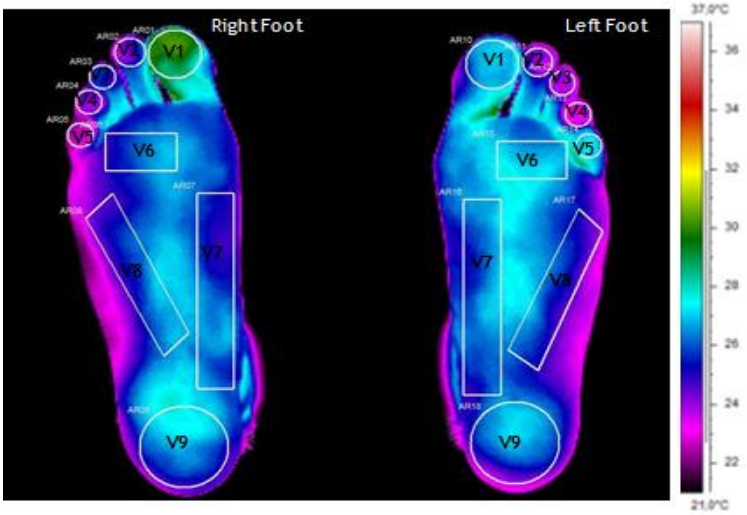


Figure 15 - ROIs of autonomic nervous system (pallet rain).



V1- First metatarsal region
V2- Second metatarsal region
V3- Third metatarsal region
V4 – Forth metatarsal region
V5- Fifth metatarsal region
V6- Arcuate region
V7- Medial region
V8- Lateral region
V9- Calcaneal region

Figure 16– Regions of interest of vascular system (pallet rain).

3.4.2.2 Statistical analysis

For the appropriate presentation of the data obtained, tables were used, with their statistical data, which will be followed by the respective analysis. Data were obtained using descriptive and inferential statistics, using SPSS-21.0 (Statistical Package for Social Sciences) software.

The Kolmogorov-Smirnov (K-S) test was used to verify if the sample follows the normal distribution. Kolmogorov-Smirnov test is used to verify the adjustment to normality of a variable of ordinal level or higher. The normal distribution is an essential requirement for the application of parametric tests. Although consulting histogram can give indications on the normal (or not) by a set of data, that assessment is often subjective, being advisable to perform the K-S test. A sample had a normal distribution if p value >0.05 [75] In order to verify the relationship between variables, if the sample follows the normal distribution the parametric test, student t-test should be used. In case of the sample do not follow the normal distribution, non-parametric tests such as Kruskal-Wallis and U Mann-Whitney are the recommended. Significance level was set at $p<0.05$. [75]

Student t-test is used to compare mean relative a certain variable, considering two groups of subjects, that is, when there are two experimental conditions involving different subjects. It is not necessary that the groups have exactly the same size, but it is desirable that there is a great imbalance. [75]

The Kruskal-Wallis H test is a rank-based nonparametric test that can be used to determine if there are statistically significant differences between two or more groups of an independent variable on a continuous or ordinal dependent variable.[76] The Mann-Whitney U test is also used to compare differences between two independent groups when the dependent variable is either ordinal or continuous, but not normally distributed. [77]

Chapter 4

Results

In this chapter, the thermal experimental results arising from the implementation of the methodology mentioned in Chapter 3 will be detailed.

4.1- Characterization of sample temperature

Regarding the sample themal characterization[2] in diabetic foot, thermographic images were collected in accordance with the capture protocol and procedure described in methodology chapter. Images were collected of total sample divided into three groups. And this data collection was made across three stages:

- 40 Healthy participants (with stimulus): images collected in 3 stages
- 14 Diabetics (with stimulus): images collected in 3 stages
- 36 Diabetics (without stimulus): images collected in 1 stage

The images collected were analyzed according to the ROIs for autonomic nervous system (ANS) and vascular system (VS) (defined in chapter 3).

[2] All temperatures presented in this study were measured in Celsius degrees (°C).

4.1.1. Sample temperature for 1st stage

In Table 7 and 8 are summarized the mean temperatures and standard deviation for autonomous nervous system and vascular system, respectively. This data refers to the mean temperatures for the first stage, i.e., without any intervention, and they were presented into two groups, healthy and diabetic participants (with and without stimulus together).

Through the observation of these data it can be verified that the healthy participants have mean temperature of ANS and VS lower than diabetic participants.

Healthy participants have a minimum mean temperature for the ANS of 26.07 ºC in region N1R and maximum of 28.01 ºC in region N6R. Diabetic participants have a minimum mean temperature for the ANS of 28.99 ºC in region N1L and maximum of 30.42 ºC in region N6R.

Table 7 – Temperature distribution in ROIs of the ANS by participant type.

ROIs of ANS	Healthy participants	Diabetic participants
N1L	26.30 ± 1.22	28.99 ± 1.83
N1R	26.07 ± 1.27	29.29 ± 1.82
N1S	0.40 ± 0.28	1.04 ± 1.00
N2L	26.61 ± 1.48	29.56 ± 1.82
N2R	26.60 ± 1.60	29.97 ± 1.97
N2S	0.42 ± 0.39	1.32 ± 1.10
N3L	26.08 ± 1.33	29.42 ± 2.13
N3R	26.23 ± 1.40	29.49 ± 1.97
N3S	0.59 ± 0.51	1.15 ± 1.00
N4+5L	26.56 ± 1.67	29.93 ± 1.98
N4+5R	26.55 ± 1.77	30.16 ± 1.94
N4+5S	0.43 ± 0.39	1.07 ± 0.67
N6L	27.99 ± 1.41	30.24 ± 1.75
N6R	28.01 ± 1.44	30.42 ± 1.66
N6S	0.48 ± 0.50	0.84 ± 0.83

In the VS, healthy individuals have a minimum mean temperature of 23.71 ºC in region V2R and maximum of 28.43 ºC in region V7R. Diabetic individuals have a minimum mean temperature of 28.13 ºC in region V2L and maximum of 30.58 ºC in region V7R.

Table 8 - Temperature distribution in ROIs of the VS by participant type.

ROIs of VS	Healthy participants	Diabetic participants
V1L	24.75 ± 2.19	29.12 ± 4.76
V1R	24.79 ± 2.32	28.41 ± 6.27
V1S	0.60 ± 0.56	1.05 ± 0.89
V2L	23.83 ±1.99	28.13 ± 6.20
V2R	23.71 ± 1.75	29.36 ± 2.19
V2S	0.56 ± 0.71	3.39 ± 7.00
V3L	23.86 ± 1.58	28.90 ± 2.19
V3R	23.80 ± 1.68	29.37 ± 2.21
V3S	0.39 ± 0.42	1.38 ± 1.25
V4L	24.05 ± 1.56	28.26 ± 4.64
V4R	24.04 ± 1.78	29.40 ± 2.24
V4S	0.42 ± 0.31	1.58 ± 1.42
V5L	24.62 ± 1.87	28.86 ± 2.15
V5R	24.47 ± 1.86	29.30 ± 2.12
V5S	0.51 ± 0.50	1.20 ± 1.00
V6L	26.70 ± 1.79	29.89 ± 2.20
V6R	26.55 ± 1.90	30.52 ± 2.32
V6S	0.48 ± 0.40	1.39 ± 1.06
V7L	28.25 ± 1.51	30.33 ± 1.71
V7R	28.43 ± 1.32	30.58 ± 1.60
V7S	0.50 ± 0.85	0.86 ± 0.89
V8L	27.56 ± 1.52	29.81 ± 1.91
V8R	27.67 ± 1.56	30.18 ± 1.83
V8S	0.50 ± 0.42	1.25 ± 0.99
V9L	26.00 ± 1.52	29.37 ± 2.22
V9R	26.08 ± 1.54	29.47 ± 2.03
V9S	0.63 ± 0.52	1.07 ± 0.94

The K-S test for the presented samples had a p value < 0.05, which means that the samples did not follow the normal distribution, so for any further statistical analysis non-parametric methods will be used.

Analysis of significance through the Mann-Whitney test to verify the relationship between healthy and diabetic participants considering the mean temperatures of the ROIs of the ANS and VS are present in table 8 and 9.

In Table 9, it is verified that healthy and diabetic individuals present statistical significance ($p<0.05$) for all regions of the ANS.

Table 9- Mann Whitney U, Wilcoxon W Z and significancy of Mann Whitney test for ANS ROIs temperatures in all partipants in 1st stage.

ROIs of ANS	U	W	Z	p
N1L	206.50	1026.50	-6.45	0.00
N1R	143.50	963.50	-6.96	0.00
N1S	489.50	1309.50	-4.16	0.00
N2L	245.50	1065.50	-6.13	0.00
N2R	194.50	1014.50	-6.54	0.00
N2S	321.00	1141.00	-5.53	0.00
N3L	176.50	996.50	-6.69	0.00
N3R	174.50	994.50	-6.71	0.00
N3S	526.00	1346.00	-3.86	0.00
N4+5L	209.00	1029.00	-6.42	0.00
N4+5R	180.50	1000.50	-6.66	0.00
N4+5S	337.00	1157.00	-5.39	0.00
N6L	303.00	1123.00	-5.66	0.00
N6R	276.50	1096.50	-5.88	0.00
N6S	532.50	1352.50	-3.81	0.00

In Table 10, it is verified that healthy and diabetic individuals present statistical significance ($p<0.05$) for all regions of the VS.

Table 10- Mann Whitney U, Wilcoxon W Z and significancy of Mann Whitney test for VS ROIs temperatures in all partipants in 1st stage.

ROIs of VS	U	W	Z	p
V1L	174.00	994.00	-6.71	0.00
V1R	240.50	1060.50	-6.17	0.00
V1S	588.00	1408.00	-3.35	0.00
V2L	163.00	983.00	-6.80	0.00
V2R	43.50	863.50	-7.77	0.00
V2S	380.00	1200.00	-5.04	0.00
V3L	59.50	879.50	-7.64	0.00
V3R	53.50	873.50	-7.69	0.00
V3S	378.00	1198.00	-5.07	0.00
V4L	113.50	933.50	-7.20	0.00
V4R	66.00	886.00	-7.59	0.00
V4S	424.00	1244.00	-4.69	0.00
V5L	147.00	967.00	-6.93	0.00
V5R	90.00	910.00	-7.39	0.00
V5S	377.00	1197.00	-5.07	0.00
V6L	268.50	1088.50	-5.94	0.00
V6R	203.50	1023.50	-6.47	0.00
V6S	375.00	1195.00	-5.09	0.00
V7L	351.00	1171.00	-5.27	0.00
V7R	304.00	1124.00	-5.65	0.00
V7S	508.50	1328.50	-4.00	0.00
V8L	348.50	1168.50	-5.29	0.00
V8R	314.00	1134.00	-5.57	0.00
V8S	429.50	1249.50	-4.64	0.00
V9L	207.50	1027.50	-6.44	0.00
V9R	188.50	1008.50	-6.59	0.00
V9S	589.00	1409.00	-3.35	0.00

4.1.2. Profile temperature for 2nd stage

In Table 11 and 12 there are summarized the mean temperatures and standard deviation for autonomic nervous system and vascular system, respectively. This data refers to the mean temperatures for the second stage, i.e., after a cold stimulus applied with a fan during 2 minutes. It was presented into two groups, healthy and diabetic participants (with stimulus).

Through the observation of these tables it can be verified that the healthy participants have mean temperature for ANS and VS ROIs lower than the diabetic participants.

Healthy participants have a minimum mean temperature for ANS of 24.93 ºC in region N3L and maximum of 26.56 ºC in region N6R. Diabetic participants have a minimum mean temperature for ANS of 28.64 ºC in region N3R and maximum of 29.84 ºC in region N6L.

Table 11- Temperature distribution in ROIs of the ANS by participants' type.

ROIs of ANS	Healthy participants	Diabetic participants
N1L	25.42 ± 0.95	28.78 ± 2.52
N1R	25.32 ± 1.08	28.77 ± 2.26
N1S	0.33 ± 0.24	0.92 ± 0.85
N2L	25.52 ± 1.06	29.47 ± 2.7
N2R	25.71 ± 1.46	29.52 ± 2.27
N2S	0.46 ± 0.54	1.24 ± 0.87
N3L	24.93 ± 1.01	29.03 ± 2.79
N3R	25.11 ± 1.15	28.64 ± 2.44
N3S	0.49 ± 0.41	1.07 ± 0.83
N4+5L	25.32 ± 1.13	29.76 ± 2.6
N4+5R	25.37 ± 1.21	29.44 ± 2.42
N4+5S	0.30 ± 0.24	1.15 ± 0.58
N6L	26.54 ± 0.87	29.84 ± 2.31
N6R	26.56 ± 1.04	29.52 ± 2.07
N6S	0.39 ± 0.43	1.12 ± 0.58

In VS, the healthy individuals have a minimum mean temperature of 22.91 ºC in region V2R and maximum of 26.86 ºC in region V7R. Diabetic individuals have a minimum mean temperature of 27.27 ºC in region V2L and maximum of 30.00 ºC in region V7L.

Table 12- Temperature distribution in ROIs of the VS by participants' type.

ROIs of VS	Healthy participants	Diabetic participants
V1L	23.70 ± 1.59	29.09 ± 2.71
V1R	23.74 ± 1.58	28.87 ± 2.70
V1S	0.48 ± 0.53	1.08 ± 0.66
V2L	22.93 ± 1.14	27.27 ± 8.15
V2R	22.91 ± 1.12	28.47 ± 2.70
V2S	0.32 ± 0.27	3.21 ± 6.56
V3L	22.97 ± 1.12	28.59 ± 2.53
V3R	22.92 ± 1.13	28.62 ± 2.41
V3S	0.25 ± 0.18	1.31 ± 0.99
V4L	23.17 ± 1.10	28.66 ± 2.82
V4R	23.16 ± 1.27	28.78 ± 2.50
V4S	0.28 ± 0.28	1.61 ± 1.30
V5L	23.58 ± 1.39	28.59 ±2.63
V5R	23.58 ± 1.50	28.87 ± 2.41
V5S	0.33 ± 0.31	1.06 ± 0.82
V6L	25.53 ± 1.33	30.08 ± 2.83
V6R	25.49 ± 1.56	30.02 ± 2.56
V6S	0.36 ± 0.27	1.33 ± 1.01
V7L	26.74 ± 0.98	30.00 ± 2.18
V7R	26.86 ± 0.98	29.62 ± 1.86
V7S	0.34 ± 0.47	1.14 ± 0.63
V8L	26.27 ± 1.08	29.78 ± 2.50
V8R	26.44 ± 1.27	29.66 ± 2.07
V8S	0.43 ± 0.33	1.26 ± 0,76
V9L	24.94 ± 1.11	29.13 ± 2.79
V9R	25.07 ± 1.29	28.75 ± 2.46
V9S	0.49 ± 0.39	1.06 ± 0.73

Analysis of significance to verify the relationship between healthy and diabetic participants through the Mann-Whitney test considering the mean temperatures in the ROIs of autonomous nervous and vascular systems to verify the independency of healthy and diabetics participants was shown in tables A and B in Appendix E.

In both tables, it can be verified that healthy and diabetic individuals present statistical significance ($p<0.05$) for all regions in the ANS and VS.

4.1.3. Profile temperature for 3rd stage

In Table 13 and 14 there are summarized the mean temperatures and standard deviation of autonomous nervous system and vascular system regions, respectively. This data refers to the mean temperatures for the third stage, i.e., after a period of 5 minutes after cold provocation to analyse the recovery response. It was presented into two groups, healthy and diabetic participants (with stimulus).

Through the observation of these tables it can be verified that the healthy participants have mean temperature of ANS and VS lower than diabetic participants.

Healthy participants have a minimum mean temperature for ANS of 24.86 ºC in region N3L and maximum of 27.01 ºC in region N6L. Diabetic individuals have a minimum mean temperature for ANS of 28.92 ºC in region N1L and maximum of 30.39 ºC in region N6L.

Table 13- Temperature distribution in ROIs of the ANS by participants' type.

ROIs of ANS	Healthy participants	Diabetic participants
N1L	25.47 ± 1.02	28.92 ± 2.70
N1R	25.24 ± 1.21	29.02 ± 2.43
N1S	0.43 ± 0.47	1.06 ± 0.94
N2L	25.64 ± 1.24	29.73 ± 2.87
N2R	25.74 ± 1.49	29.89 ± 2.42
N2S	0.39 ± 0.32	1.31 ± 1.16
N3L	24.86 ± 1.15	29.46 ± 3.06
N3R	25.07 ± 1.44	29.11 ± 2.66
N3S	0.54 ± 0.58	1.22 ± 1.05
N4+5L	25.54 ± 1.51	30.13 ± 2.78
N4+5R	25.35 ± 2.75	29.86 ± 2.50
N4+5S	0.76 ± 2.00	1.10 ± 0.74
N6L	27.01 ± 1.05	30.39 ± 2.46
N6R	26.94 ± 1.21	30.12 ± 2.09
N6S	0.29 ± 0.32	0.98 ± 0.59

In the VS, healthy individuals have a minimum mean temperature of 22.98 ºC in region V2L and maximum of 27.22 ºC in region V7R. Diabetic participants have a minimum mean temperature of 27.88 ºC in region V2L and maximum of 30.51 ºC in region V6L.

Table 14- Temperature distribution in ROIs of the VS by participants' type.

ROIs of VS	Healthy participants	Diabetic participants
V1L	23.93 ± 2.63	29.45 ± 2.96
V1R	24.27 ± 2.93	29.18 ± 2.89
V1S	0.72 ± 1.40	1.24 ± 1.11
V2L	22.98 ± 1.92	27.88 ± 8.43
V2R	23.18 ± 1.91	28.79 ± 2.68
V2S	0.64 ± 1.34	3.56 ± 6.69
V3L	23.06 ± 1.73	29.02 ± 2.94
V3R	23.13 ± 1.89	28.94 ± 2.57
V3S	0.35 ± 0.39	1.53 ± 1.46
V4L	23.39 ± 1.88	29.03 ± 3.05
V4R	23.36 ± 2.08	29.20 ± 2.60
V4S	0.40 ± 0.54	1.91 ± 1.50
V5L	23.78 ± 1.96	29.00 ± 2.97
V5R	23.76 ± 2.17	29.19 ± 2.53
V5S	0.48 ± 0.63	1.24 ± 1.24
V6L	25.63 ± 1.57	30.51 ± 3.03
V6R	25.65 ± 2.02	30.36 ± 2.63
V6S	0.54 ± 0.55	1.49 ± 1.11
V7L	27.19 ± 1.18	30.48 ± 2.31
V7R	27.22 ± 1.31	30.19 ± 1.90
V7S	0.44 ± 0.70	0.97 ± 0.74
V8L	26.46 ± 1.23	30.05 ± 2.69
V8R	26.57 ± 1.40	30.06 ± 2.22
V8S	0.44 ± 0.32	1.27 ± 1.05
V9L	24.86 ± 1.28	29.50 ± 3.11
V9R	25.03 ± 1.34	29.24 ± 2.74
V9S	0.49 ± 0.37	1.17 ± 1.03

Analysis of significance through the Mann-Whitney test considering mean temperatures of ROIs for autonomous nervous and vascular systems for testing the independence between healthy and diabetics participants was shown in table C and D in Appendix F.

In both tables, it is verified that healthy and diabetic individuals present statistical significance ($p<0.05$) of independence for all regions of the ANS and VS.

The Figures 17 illustrates thermal images from a healthy individual and Figure 18 a diabetic individual over the three stages of the study, respectively. In these thermal images it is very visible a variation of feet temperature during data collection.

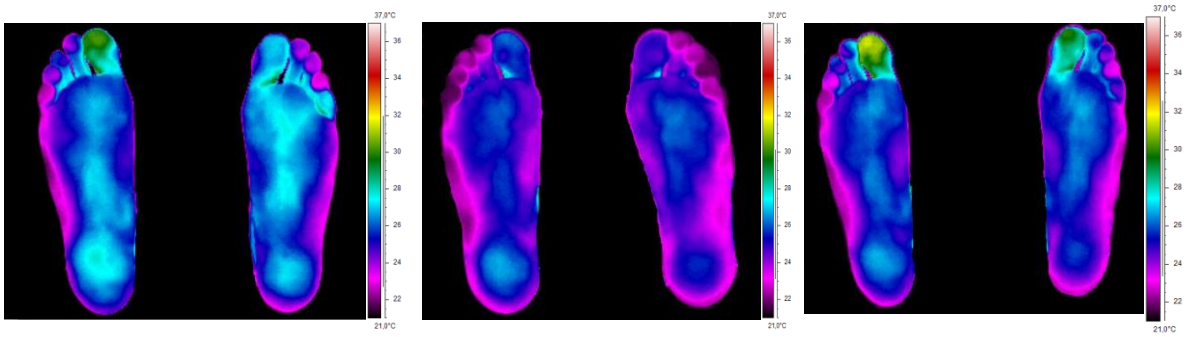


Figure 17- Thermal images of the feet of a healthy individual over the three stages.

Figure 18- Thermal images of the feet of a diabetic individual over the three stages.

Thermal Images of the feet were collected in three stages in order to understand the thermophysiology in a healthy foot and a diabetic foot when suffering a bodily imbalance.

This physiological response may be measurable, and the ROIs mean temperature of both systems are presented in figures 19 and 20 for a healthy and diabetic feet.

In the Figure 19, for the ANS, it is observed that for healthy individuals there was a decrease of 1.1°C in the second stage and an increase of 0.1°C after the third stage. Diabetic individuals experienced a decrease of 0.2°C in the second stage and an increase of 0.4°C in the third stage.

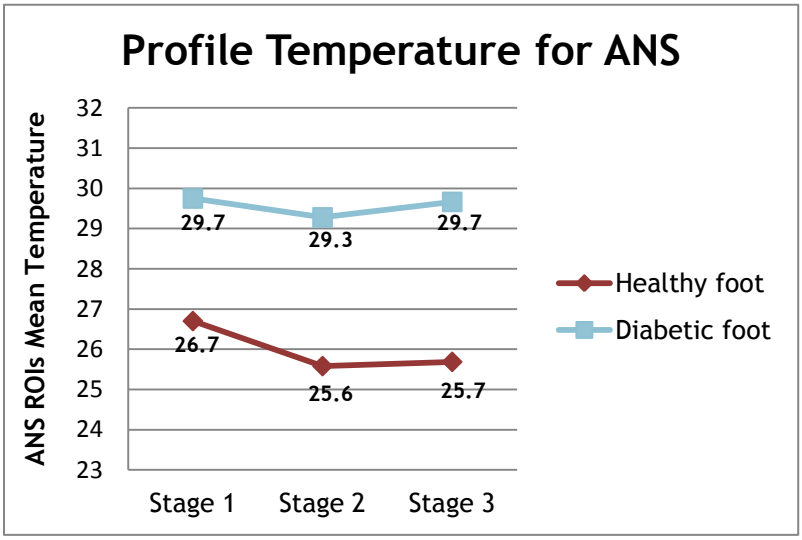


Figure 19- Variation of the mean temperature of ROIs of autonomous nervous system throughout the three stages of healthy and diabetic feet.

In Figure 20, for the VS, it is observed that for healthy individuals there was a decrease of 1.1°C in the second stage and an increase of 0.2°C after the third stage. Diabetic individuals experienced a decrease of 0.4°C in the second stage and an increase of 0.4°C in the third stage.

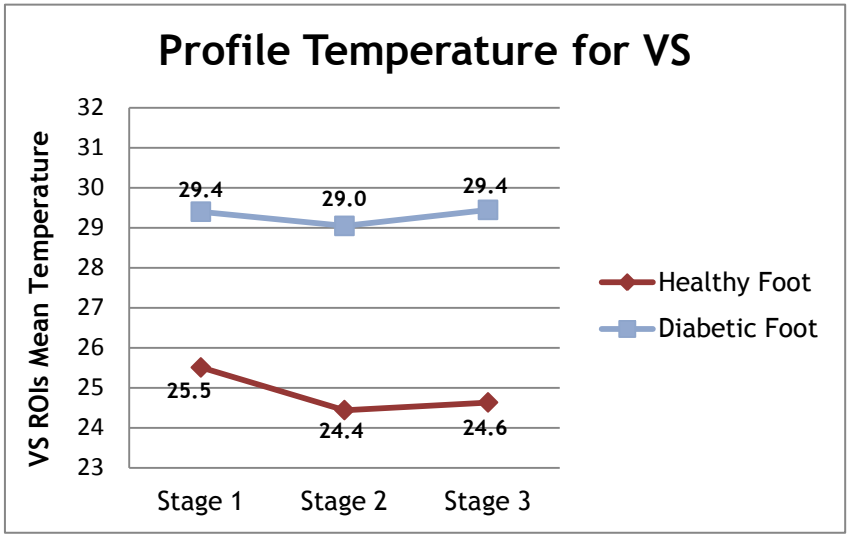


Figure 20- Variation of the mean temperature of ROIs of vascular system throughout the three stages of a healthy and diabetic feet.

For a better understanding of the impact of the stimulus and the responsiveness of the temperature recovery, the temperature difference for the various ROIs was calculated. These values were calculated through the difference between mean temperature ROIs of Stage 2 and Stage 1, and the difference between Stage 3 and Stage 1, for healthy and diabetic individuals. Table 15 shows the different values for ANS ROIs, where the values of minimal and maximal difference for healthy and diabetic indviduals are highlighted.

And in Table 16 there are presented the values of difference between stages for VS ROIs, where the values of minimal and maximal difference for healthy and diabetic indviduals are highlighted.

Table 15- Difference of mean temperatures of ANS ROIs for healthy and diabetic participants.

	Healthy Participants	Healthy Participants	Diabetic Participants	Diabetic Participants
ROIs of ANS	S2-S1	S3-S1	S2-S1	S3-S1
N1L	-0.88	-0.83	-0.21	-0.07
N1R	-0.75	-0.83	-0.52	-0.27
N2L	-1.09	-0.97	-0.09	0.17
N2R	-0.89	-0.86	-0.45	-0.08
N3L	-1.15	-1.22	-0.39	0.04
N3R	-1.12	-1.16	-0.85	-0.38
N4+5L	-1.24	-1.02	-0.17	0.2
N4+5R	-1.18	-1.2	-0.72	-0.3
N6L	-1.45	-0.98	-0.4	0.15
N6R	-1.45	-1.07	-0.9	-0.3

Table 16- Difference of mean temperatures of VS ROIs for healthy and diabetic participants.

	Healthy Participants	Healthy Participants	Diabetic Participants	Diabetic Participants
ROIs of ANS	S2-S1	S3-S1	S2-S1	S3-S1
V1L	-1.05	-0.82	-0.03	0.33
V1R	-1.05	-0.52	0.46	0.77
V2L	-0.9	-0.85	-0.86	-0.25
V2R	-0.8	-0.53	-0.89	-0.57
V3L	-0.89	-0.8	-0.31	0.12
V3R	-0.88	-0.67	-0.75	-0.43
V4L	-0.88	-0.66	0.4	0.77
V4R	-0.88	-0.68	-0.62	-0.2
V5L	-1.04	-0.84	-0.27	0.14
V5R	-0.89	-0.71	-0.43	-0.11
V6L	-1.17	-1.07	0.19	0.62
V6R	-1.06	-0.9	-0.5	-0.16
V7L	-1.51	-1.06	-0.33	0.15
V7R	-1.57	-1.21	-0.96	-0.39
V8L	-1.29	-1.1	-0.03	0.24
V8R	-1.23	-1.1	-0.52	-0.12
V9L	-1.06	-1.14	-0.24	0.13
V9R	-1.01	-1.05	-0.72	-0.23

4.2. Relation between diabetic foot temperature and diabetic foot ulcer

Diabetic participants had different types of feet ulcer. These can be denominated neuropathic, ischaemic, and neuroischaemic depending on their origin. Therefore, because of this variability in pathology of diabetic foot, it was studied if there is any relationship between foot ROIs temperature and type of ulcer. Three cases were studied:

a) Ulcer neuropathic vs ulcer ischaemic
b) Ulcer neuropathic vs ulcer neuroischaemic
c) Ulcer ischaemic vs ulcer neuroischaemic

4.2.1. Ulcer neuropathic vs ulcer ischaemic

Analysis of the Independence between diabetics participants with neuropathic and ischaemic ulcers through the Mann-Whitney test considering the mean temperatures in ROIs for autonomic nervous and vascular systems is shown in table 17 and 18 respectively.

In table 17, it is verified that diabetic participants with neuropathic and ischaemic ulcers do not present statistical significance ($p>0.05$) of Independence for any region of ANS.

Table 17- Mann Whitney U, Wilcoxon W Z and significancy of Mann Whitney test for ANS ROIs temperatures of partipants with neuropathic and ischaemic ulcers.

ROIs of ANS	U	W	Z	p
N1L	30.00	33.00	0.00	1.00
N1R	29.00	494.00	-0.08	0.94
N1S	28.00	31.00	-0.16	0.88
N2L	26.00	29.00	-0.31	0.76
N2R	25.00	490.00	-0.39	0.70
N2S	16.00	481.00	-1.09	0.28
N3L	30.00	33.00	0.00	1.00
N3R	23.00	26.00	-0.55	0.59
N3S	18.00	483.00	-0.94	0.35
N4+5L	24.00	27.00	-0.47	0.64
N4+5R	29.50	494.50	-0.04	0.97
N4+5S	18.00	483.00	-0.94	0.35
N6L	24.00	27.00	-0.47	0.64
N6R	28.00	31.00	-0.16	0.88
N6S	24.50	489.50	-0.43	0.67

In table 18, it is verified that diabetic participants with neuropathic and ischaemic ulcers only present statistical significance ($p<0.05$) of Independence in one region, V3S, of vascular system.

Table 18- Mann Whitney U, Wilcoxon W Z and significancy of Mann Whitney test for VS ROIs temperatures of partipants with neuropathic and ischaemic ulcers.

ROIs of VS	U	W	Z	p
V1L	19.00	22.00	-0.86	0.39
V1R	29.00	494.00	-0.08	0.94
V1S	26.00	491.00	-0.31	0.76
V2L	27.00	30.00	-0.23	0.82
V2R	30.00	33.00	0.00	1.00
V2S	20.00	485.00	-0.78	0.44
V3L	13.00	16.00	-1.32	0.19
V3R	26.50	491.50	-0.27	0.79
V3S	2.00	467.00	-2.18	0.03
V4L	12.00	15.00	-1.40	0.16
V4R	26.00	491.00	-0.31	0.76
V4S	3.00	468.00	-2.11	0.04
V5L	17.00	20.00	-1.01	0.31
V5R	23.50	26.50	-0.51	0.61
V5S	21.00	486.00	-0.70	0.48
V6L	24.00	27.00	-0.47	0.64
V6R	23.00	488.00	-0.55	0.59
V6S	11.00	476.00	-1.48	0.14
V7L	24.00	27.00	-0.47	0.64
V7R	26.50	29.50	-0.27	0.79
V7S	29.50	32.50	-0.04	0.97
V8L	28.00	31.00	-0.16	0.88
V8R	26.00	491.00	-0.31	0.76
V8S	29.50	32.50	-0.04	0.97
V9L	29.50	494.50	-0.04	0.97
V9R	25.00	28.00	-0.39	0.70
V9S	20.00	485.00	-0.78	0.44

4.2.2. Ulcer neuropathic vs ulcer neuroischaemic

Analysis of significance of the Independence between diabetics participants with neuropathic and neuroischaemic ulcers through through the Mann-Whitney test considering

the mean temperatures of ROIs for autonomic nervous and vascular systems is shown tables E and F of Appendix G.

In this tables E and F of Appendix G, it can be verified that diabetic participants with neuropathic and neuroischaemic ulcers do not present statistical significance ($p>0.05$) of independence for any region of the ANS and the VS.

4.2.3. Ulcer ischaemic vs ulcer neuroischaemic

Analysis of significance of the Independence between diabetics participants with ischaemic and neuroischaemic ulcers through through the Mann-Whitney test considering the mean temperatures in ROIs for autonomous nervous and vascular systems are shown in tables G and H of APPENDIX H.

In this tables G and H of Appendix H, it can be verified that diabetic individuals with ischaemic and neuroischaemic ulcers do not present statistical significance ($p>0.05$) of independence for any region of the ANS and the VS.

The figure 21 illutrates the thermal and visible images of feet with neuropathic, ischaemic and neuroischaemic ulcers, where can be visualized their differences of temperature distribution.

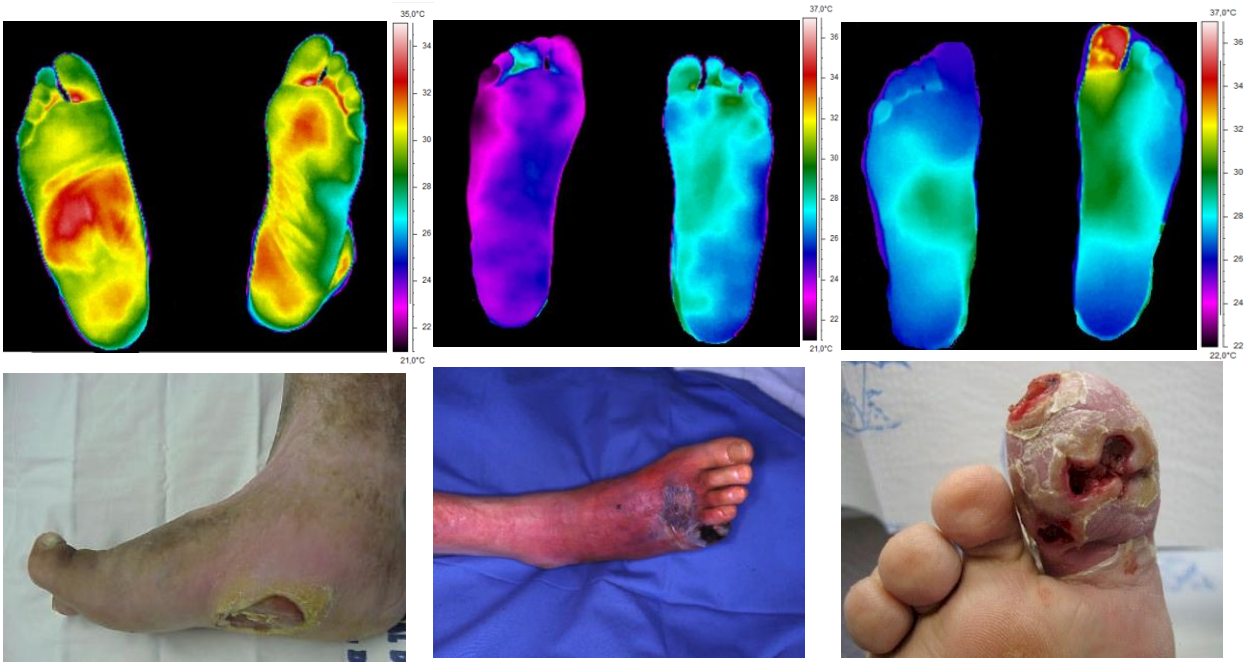


Figure 21- Thermal and visual images of a neuropathic, ischaemic and neuroischaemic ulcers.

4.3. Relation between foot temperature and characteristics of individuals

To study the relation between the diferente population characteristics and the type of participants, the following comparisons were performed:

a) Different type of diabetes

b) Healthy and diabetic individuals with different glicemia interval

c) Healthy and diabetic individuals with different BMI classification

d) Healthy and diabetic individuals with different age group

Tested whether these variables have or not statistical significance when analyzed for the mean temperature in ROIs of autonomic nervous and vascular system.

4.3.1. Different type of diabetes

In the group of participants with diabetes, there are individuals who differ in the type of diabetes (type 1 and type 2), it was investigated if there is any relationship between temperature of the various feet ROIs for ANS and VS and type of diabetes.

Analysis of significance of the relation between mean temperatures in ROIs of ANS and VS with type of diabetes through Mann-Whitney test is shown in table 19 and 20.

In table 19, it can be verified that individuals with diabetes type 1 or type 2 present statistical significance ($p<0.05$) for region N4+5R of the ANS.

Table 19 - Mann Whitney test for different type of diabetes in the ANS.

ROIs of ANS	U	W	Z	p
N1L	265.50	565.50	-0.69	0.49
N1R	201.00	501.00	-1.98	0.05
N1S	274.00	574.00	-0.52	0.60
N2L	281.00	581.00	-0.38	0.70
N2R	209.00	509.00	-1.82	0.07
N2S	243.50	543.50	-1.13	0.26
N3L	265.50	565.50	-0.69	0.49
N3R	212.50	512.50	-1.75	0.08
N3S	255.50	555.50	-0.89	0.37
N4+5L	299.50	624.50	-0.01	0.99
N4+5R	190.50	490.50	-2.19	0.03
N4+5S	241.50	541.50	-1.17	0.24
N6L	294.00	594.00	-0.12	0.90
N6R	210.50	510.50	-1.79	0.07
N6S	283.50	583.50	-0.33	0.74

In table 20, it can be verified that individuals with diabetes type 1 or type 2 present statistical significance ($p<0.05$) for region V1R of the VS.

Table 20- Mann Whitney test for different type of diabetes in the VS.

ROIs of VS	U	W	Z	p
V1L	286.00	611.00	-0.28	0.78
V1R	196.50	496.50	-2.07	0.04
V1S	294.50	619.50	-0.11	0.91
V2L	272.50	597.50	-0.55	0.58
V2R	227.50	527.50	-1.45	0.15
V2S	272.50	572.50	-0.55	0.58
V3L	285.50	585.50	-0.29	0.77
V3R	200.50	500.50	-1.99	0.05
V3S	208.00	508.00	-1.84	0.07
V4L	281.00	581.00	-0.38	0.70
V4R	212.50	512.50	-1.75	0.08
V4S	219.50	519.50	-1.61	0.11
V5L	279.00	579.00	-0.42	0.67
V5R	238.00	538.00	-1.24	0.22
V5S	226.00	526.00	-1.48	0.14
V6L	279.50	579.50	-0.41	0.68
V6R	207.50	507.50	-1.85	0.06
V6S	234.50	534.50	-1.31	0.19
V7L	285.50	585.50	-0.29	0.77
V7R	229.50	529.50	-1.41	0.16
V7S	256.50	556.50	-0.87	0.38
V8L	283.00	583.00	-0.34	0.73
V8R	217.00	517.00	-1.66	0.10
V8S	300.00	600.00	0.00	1.00
V9L	264.50	564.50	-0.71	0.48
V9R	205.00	505.00	-1.90	0.06
V9S	226.50	526.50	-1.47	0.14

4.3.2. Different glicemia interval

Since this study approaches a condition associated with diabetes, it was measured the glycemic index of participants, and depending on its value, they were included in a glicemia classification (>100, 100-124 and ≥125 mg/dl).

Analysis of significance of the glicemia intervals through the Kruskal-Wallis test based in the comparison of the mean temperature in ROIs of ANS and VS is data shown in Tables 21 and 22.

In table 21, it can be verified that the healthy participants with different glucose value do not present any significance statistical ($p>0.05$) of independence for regions of ANS. And the diabetics participants have only presented statistical significance for the region N4+5R of the ANS.

Table 21- Different glicemia interval and ANS.

	Healthy Participants	Diabetic Participants
ROIs of ANS	p	p
N1L	0.12	0.26
N1R	0.16	0.10
N1S	0.05	0.98
N2L	0.33	0.27
N2R	0.16	0.09
N2S	0.08	0.86
N3L	0.33	0.19
N3R	0.83	0.31
N3S	0.13	0.64
N4+5L	0.39	0.10
N4+5R	0.34	0.04
N4+5S	0.34	0.59
N6L	0.57	0.26
N6R	0.31	0.11
N6S	0.57	0.21

In table 22, it can be verified that the healthy participants with different glucose value do not present any significance statistical ($p>0.05$) independence for regions of the VS. And the diabetics participants have presented statistical significance in regions V1L, V3R, V4R, V5R and V6R of the VS

Table 22- Different glicemia interval and VS.

	Healthy participants	Diabetic Participants
ROIs of VS	p	p
V1L	0.20	0.02
V1R	0.21	0.06
V1S	0.21	0.53
V2L	0.18	0.19
V2R	0.16	0.09
V2S	0.19	0.69
V3L	0.19	0.06
V3R	0.19	0.02
V3S	0.05	0.09
V4L	0.23	0.15
V4R	0.17	0.01
V4S	0.54	0.64
V5L	0.19	0.16
V5R	0.24	0.02
V5S	0.11	0.93
V6L	0.55	0.21
V6R	0.45	0.02
V6S	0.20	0.79
V7L	0.23	0.28
V7R	0.30	0.14
V7S	0.77	0.19
V8L	0.34	0.43
V8R	0.23	0.09
V8S	0.37	0.53
V9L	0.36	0.37
V9R	0.85	0.37
V9S	0.11	0.60

4.3.3. Different BMI classification

Two of the variables collected during this study were the height and weight of each participant. These two values were useful to calculate the body mass índex (equation 1). After this calculus, participants were included in a BMI classification, 18.5<25, 25<30, 30<35 or ≥35.

Analysis of significance of the BMI classification through the Kruskal-Wallis test based in the comparison of the mean temperature in ROIs of ANS and VS is shown in Tables 23 and 24.

In table 23, it can be verified that for the healthy participants with different BMI classification do not present any significance statistical ($p>0.05$) of independence for regions of the ANS. And the diabetics participants have presented statistical significance ($p<0.05$) in regions N1R, N2R, N4+5R and N6R of the ANS.

Table 23- Different BMI classification and ANS.

	Healthy Participants	Diabetic Participants
ROIs of ANS	**p**	**p**
N1L	0.50	0.44
N1R	0.97	0.02
N1S	0.14	0.91
N2L	0.74	0.45
N2R	0.93	0.01
N2S	0.51	0.88
N3L	0.56	0.40
N3R	0.75	0.10
N3S	0.68	0.63
N4+5L	0.65	0.23
N4+5R	0.84	0.02
N4+5S	0.13	0.82
N6L	0.29	0.28
N6R	0.79	0.02
N6S	0.89	0.79

In table 24, it can be verified that the healthy participants with different BMI classification do not present any statistical significance ($p>0.05$) of independence for regions of the VS. And the diabetics participants have presented statistical significance ($p<0.05$) of independence for the regions V2R, V3R, V4R, V5R, V6R, V7R and V8R of the VS.

Table 24- Different BMI classification and VS.

	Healthy participants	Diabetic Participants
ROIs of VS	p	p
V1L	0.48	0.32
V1R	0.66	0.21
V1S	0.40	0.40
V2L	0.90	0.42
V2R	0.90	0.02
V2S	0.78	0.75
V3L	0.70	0.43
V3R	0.63	0.02
V3S	0.16	0.95
V4L	0.62	0.75
V4R	0.65	0.03
V4S	0.68	0.35
V5L	0.69	0.58
V5R	0.36	0.04
V5S	0.37	0.55
V6L	0.84	0.42
V6R	0.68	0.03
V6S	0.92	0.96
V7L	0.66	0.36
V7R	0.89	0.02
V7S	0.19	0.60
V8L	0.36	0.48
V8R	0.87	0.01
V8S	0.04	0.53
V9L	0.71	0.44
V9R	0.95	0.14
V9S	0.55	0.91

4.3.4. Different age group

Other variable that was collected during the study was the participants age, and depending on its value was included in a age group (18-29, 30-39, 40-49, 50-59, 60-69, ≥70 years).

Analysis of significance of the age group through the Kruskal-Wallis test based in the comparison of the mean temperature in ROIs of ANS and VS is shown in Tables 25 and 26.

In table 25, it can be verified that both groups of healthy and diabetics participants with different age groups do not present any statistical significance ($p>0.05$) of independence for regions of the ANS.

Table 25- Different age groups and ANS

	Healthy Participants	Diabetic Participants
ROIs of ANS	p	p
N1L	0.23	0.11
N1R	0.23	0.48
N1S	0.19	0.57
N2L	0.18	0.17
N2R	0.24	0.45
N2S	0.23	0.66
N3L	0.83	0.08
N3R	0.83	0.16
N3S	0.60	0.27
N4+5L	0.39	0.12
N4+5R	0.39	0.54
N4+5S	0.73	0.57
N6L	0.36	0.18
N6R	0.34	0.31
N6S	0.13	0.44

In table 26, it can be verified that healthy participants with different age groups do not present any statistical significance ($p>0.05$) of independence for regions of the VS. And the diabetics participants have statistical significance ($p<0.05$) of independence for regions V1L, V3R,V4R, V5R and V6R of the VS.

Table 26- Different age groups and VS.

	Healthy participants	Diabetic Participants
ROIs of VS	p	p
V1L	0.20	0.02
V1R	0.21	0.06
V1S	0.21	0.53
V2L	0.18	0.19
V2R	0.16	0.09
V2S	0.19	0.69
V3L	0.19	0.06
V3R	0.19	0.02
V3S	0.05	0.09
V4L	0.23	0.15
V4R	0.17	0.01
V4S	0.54	0.64
V5L	0.19	0.16
V5R	0.24	0.02
V5S	0.11	0.93
V6L	0.55	0.21
V6R	0.45	0.02
V6S	0.20	0.79
V7L	0.23	0.28
V7R	0.30	0.14
V7S	0.77	0.19
V8L	0.34	0.43
V8R	0.23	0.09
V8S	0.37	0.53
V9L	0.36	0.37
V9R	0.85	0.37
V9S	0.11	0.60

4.4. Thermal symmetry

According to the literature, it was confirmed that the lower limbs of the human body have a thermal symmetry (|thermal symmetry|≤0,5) [67, 68]. This crucial information allows a greater understanding and better identification of foot injuries. Therefore thermal symmetry, calculated through the equation 2 (chapter 3), was studied for the feet of healthy individuals and compared with diabetic individuals. This information is presented in figures 22 and 23, in which it can be observed that for both systems (autonomic nervous system and

vascular system) healthy individuals exhibit thermal symmetry, opposite to diabetics who have very different temperatures on the feet.

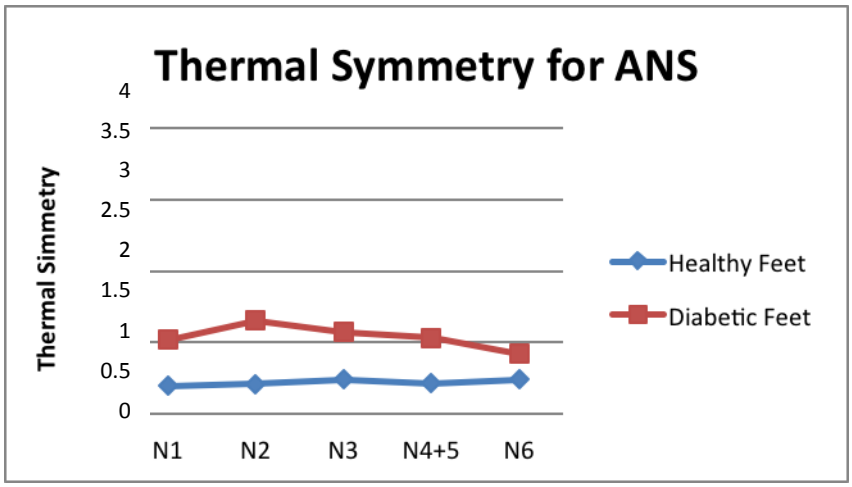


Figure 22- Thermal symmetry for ANS.

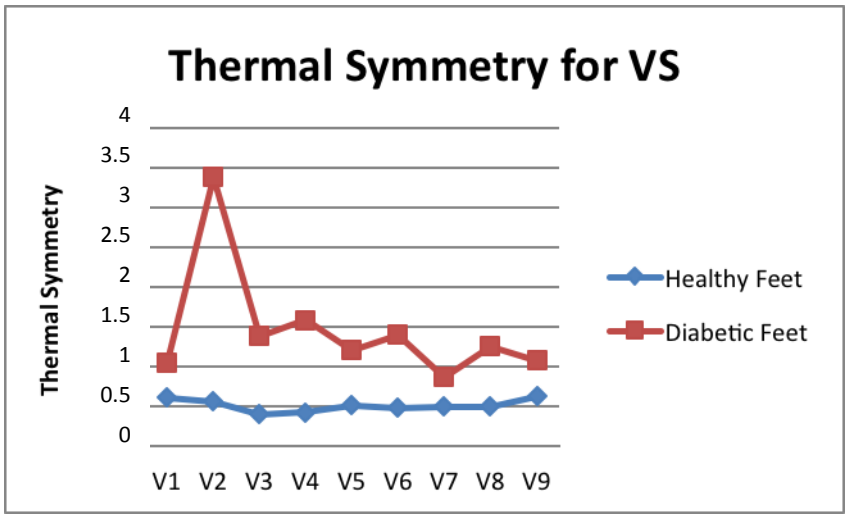


Figure 23- Thermal symmetry for VS.

This huge discrepancy between the values of thermal symmetry between healthy individuals and diabetics, it can be easily observed through the figure 24. The thermal images A and B are of healthy individuals where it can be noticed the symmetrical pattern. Thermal Images C and D are of individuals with diabetic foot injuries, which exhibit marked differences in symmetry patterns, due to ulcers resulting from diabetes.

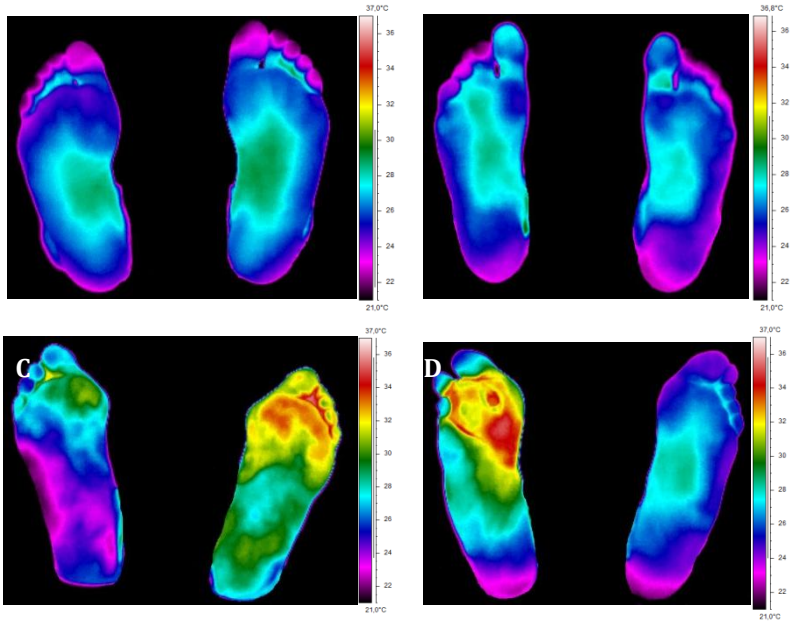


Figure 24- Thermal images of healthy individuals (A and B). Thermal images of individuals with diabetic foot (C and D).

4.5. Follow-up

Due to the severity of diabetic foot lesions, follow-up and constant monitoring of patients treatment is necessary. The values of thermal symmetry are an important parameter to assess the progression of lesions identified and adjust the respective treatment.

To corroborate that thermography is an ideal monitoring method, the values of thermal symmetry for a follow-up of a patient, that has been followed for 3 weeks, is presented in figure 25, it can be observed that the patient has presented an improvement from his injury in the second week and a slight increase in the third week.

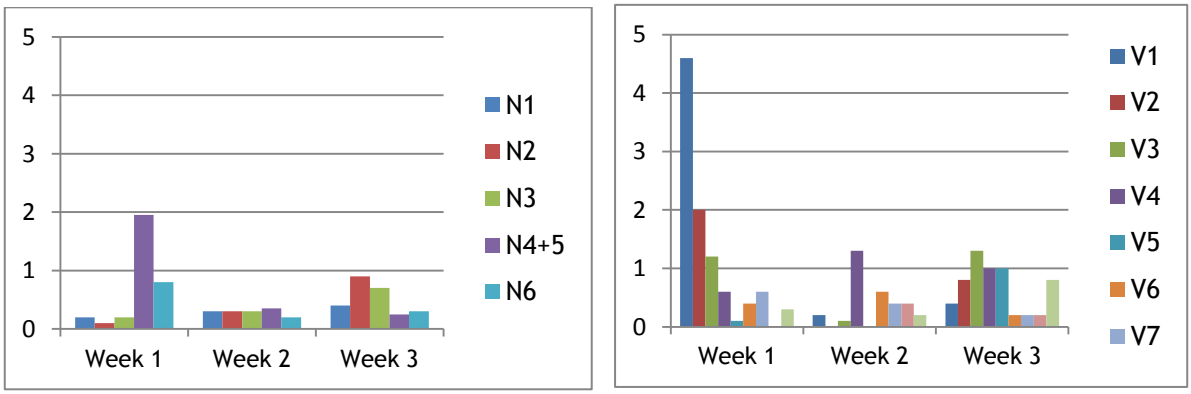


Figure 25- Results of thermal symmetry during a 3 weeks follow-up of a diabetic patient.

4.5. Summary

In the baseline diabetic patients presented higher mean temperature (approximately 3°C) in the ROIs of both systems when compared to healthy participants. A cold stimulus provoked a greater decrease of mean temperature in ANS and VS systems for healthy participants than for diabetic participants. Medial foot regions present more significance statistical when compared the mean temperature ROIs of autonomous nervous and vascular systems. Glicemia interval, BMI classification and age group may be predictors of statistical signficance between ANS and VS regions of interest.

Chapter 5

Discussion

In the last decades considerable progress has been made in the performance of infrared imaging, equipment, standardisation of technique and clinical protocols for thermal imaging.

This improvements were useful for a better understanding about physiological mechanisms and of temperature distribution on the body surface, allowing a wider aceptance of thermography by the health professionals.

A methodology for studing surface skin temperature of the plantar feet was designed, implemented and assessed. ROIs have been defined for characterize the autonomous nervous and vascular systems in the plantar feet. These ROIs where useful for characterizing the temperature distribution, identify healthy controls and diabetic patients, distinguish diferente ulcer type and the influence of the characteristics that influence the pathology.

However, despite all the care taken, thermal images capture in CHP showed values of mean humidity superior to adequate (humidity>50%). Despite this not being an impediment to image capture, it is important to consider because it can be a source of error.

To study and characterize the temperature of the foot, a cold stimulus was applied to the feet of the participants, in order to provoke an imbalance in the feet temperature and study its physiological response.

In the first moment diabetic patients presented higher mean temperature in the ROIs of both systems when compared to healthy participants. Inflammation in the feet associated with diabetic foot pathology can cause this fairly significant difference (approximately 3°C between healthy and diabetic for ANS and VS) in mean temperature.

Through the detailed analysis of the mean temperatures of the ROIs of autonomous nervous system, it is verified that healthy and diabetic individuals have a lower temperature for the sural area of the foot (N1) and for a higher temperature for saphenous area (N6).

In mean temperature of the ROIs of vascular system, it is verified that healthy and diabetic participants have a lower temperature for the second metatarsal of the foot (V2) and higher temperature in medial region of the foot (V7).

This difference in temperatures for the aforementioned ROIs is due to the fact that the source of foot blood irrigation is closer in some regions, such as N6 and V7 that are medial plantar regions than others, such as N1 and V2, that are also areas of greater thermal energy release, which can lead to a lower mean temperature.

After application of a cold stimulus during 2 minutes, is was verified that there was a mean temperature decrease of 1.1°C for healthy individuals and 0.4 to 0.6°C for diabetic individuals. This decrease of temperature is not very noticeable, because the used fan had little power and the affected area was not covered equally.

Diminuishing the temperature of the feet was not constant for all areas, however, both groups of healthy and diabetic subjects have a greater cooling to the ROIs corresponding to medial area of foot (N6 for the autonomous nervous system and V7 in vascular system). This areas are most sensible to temperature variation due the fact that have higher blood irrigation.

In the third moment, in order to understand the responsiveness of temperature recovery after an imbalance caused by the cold stimulus, the healthy participants experienced a mean temperature increase of about 0.1-0.2°C in relation to the previous moment, and the temperature of the feet of diabetic individuals increased approximately 0.5°C.

The ROIs of healthy subjects where the highest occured was the N6 in the autonomous nervous system and V7 of vascular system. Diabetic individuals had a greater temperature increase in N6 and V6 for autonomic nervous and vascular systems, respectively. This ROIs are located in the inner region of the plantar feet, which is closer either to the main blood and nervous sources.

After studying the relationship of the mean temperature foot ROIs between individuals with different types of diabetic foot lesion (neuropathic, ischaemic and neuroischaemic), it was concluded that there was no statistical evidence of a direct relationship between the ROIs temperature and the type of ulcer. However, this may be, due to several factors, such as the sample dimension. Another limitation of this study was the impossibility of applying a cold stimulus in a large part of diabetic individuals, due to practical constraints in the collection site, and it has limited the study in their physiologic response over three stages.

This study was pioneer in characterizing the planar foot temperature distribution in two separate physiological systems of the diabetic foot, and in relating it with several variables.

Through the analysis of the several ROIs mean temperature for the autonomous nervous and vascular systems for diabetic individuals with type 1 or type 2 diabetes, there was only found a statistical significance in two regions (N4+5 of autonomic nervous system and V1 of vascular system). Within 15 studied ROIs, it was only found statistical evidence in two, those to ROIs are located in the region of the hallux, which is one of the most affected areas with the studied condition, for a better conclusion in the other ROIs, a larger sample and a thermal stimulus is advised.

Since, continuous monitoring of blood glucose values in diabetics is a relevant procedure to have it controlled within the suitable range, to prevent diabetes progression and all its complications associated. With this characteristic, for the diabetic patients it was found statistical significance in the medial region (N4+5) of autonomous nervous system and in first, third, forth, fifth and arcuate foot regions (V1, V3, V4, V5 and V6) of vascular system. This can be explained by the associated ROIs with the condition and the glicemia interval being one of the most affect areas with ulcers, since it is close to the blood and nervous branches to the toes. For healthy individuals, it was not found any statistical evidence for any region of interest in both physiological systems. However, since the blood glucose value was not measured under the same conditions for all individuals (fasting period), that can be a bias.

Regarding the relation with body mass index, it was found that this variable was not statistically significant for healthy participants in both physiological systems, however it is statistically significant in diabetic patients in all regions of the autonomous nervous system, and all regions of vascular system excluding the V1 and V9. These findings, indicate that the the body mass index is an important factor when studied the temperature of the feet of diabetic individuals. Moreover, a high value of BMI is a risk factor for diabetes and other health complications.

The relationship with age group and condition did not present statistical significance with health participants. For diabetic patients, no statistical evidence was found for any regions of autonomic nervous system. For the vascular system it was found statistical significance in the V1, V3, V4, V5 and V6 regions. This may indicate that age might be a predictor of the temperature difference for the foot ROIs close to the blood and nervous branches that feed the toes, already mentioned as an high risk area for diabetic foot disease. Age brings an enormous panoply of complications such as longer period of disease, vascular problems, more difficulties in people keeping healthy habits, hygiene and self-care issues, becoming and important factor to take into consideration in the development of diabetic foot.

In this study sample most of the affected patients revealed a higher incidence of diabetic foot in the right limb than in the other, which explains the obtained results per region having a greater tendency to the right side.

Thermal symmetry is a fundamental indicator of the state of health of individuals. In the present study the thermal symmetry was used to corroborate with previous studies, in which

|thermal symmetry| ≤ 0.5°C when compared the difference temperature between left and right foot [67,68]. This indicator confirmed the presence of pathology in the diabetic patients.

Constant monitoring of individuals with diabetic foot ulcers is essential for monitoring the state of injury and if needed adjust treatment. Through the monitoring of a patient in CHP, it was possible to verify the progression of its treatment. Thus, thermography presents itself as a efficient tool for monitoring since it causes no harm to the patients and allows the tracking of patients over a long period of time without any injurious effect in them Being a tool that allows a real time analysis it can have a important diagnostic information during the patient appointment and also help clinicians to decide about the viability of the tissue in an amputation decision.

Thermal imaging needs to evaluate in some technological aspects such as software, since there is no standard image format or capture and analysis software, having the analysis being performed in a manual way.

Chapter 6

Conclusion

The aim of this research project was to develop a methodology for characterizing the skin temperature of the plantar feet in diabetic foot patients. It was completely fulfilled, a capture analysis protocol was designed, implemented and assessed.

Static and dynamic reference values of the plantar feet from a healthy population were provided. A thermal stimulus method was investigated and a relation between several characteristics that could affect the diabetic foot were explored and identified along with the proposed methodology.

The main findings of this research project were:

In the baseline diabetic patients presented higher mean temperature (approximately 3°C) in the ROIs of autonomous nervous and vascular systems when compared to healthy participants. A cold stimulus provoked a greater decrease of mean temperature in ANS and VS systems for healthy participants than for diabetic participants.

Medial foot regions present more statistical significance when compared the mean temperature ROIs of autonomous nervous and vascular systems.

Glicemia interval, BMI classification and age group may be predictors of statistical signficance between ANS and VS regions of interest.

6.1 Proposed future work

In order to take this work into a next stage, the following future work is proposed:

- Apply this methodology in a larger dimension experiment, to obtain more reliable results.
- Develop an efficient cold stimulus for better understanding of the thermophysiology of the diabetic feet and associated characteristics.
- Development of a dedicated software for standardizing the image analysis in order to improve the reproducibility and accuracy of the method.
- Investigate indicators such as thermal symmetry for diabetic foot treatments assessment.

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APPENDIX A

centro hospitalar do Porto

Hospital Santo António | Hospital Maria Pia | Maternidade Júlio Dinis | Hospital Joaquim Urbano

Largo Prof. Abel Salazar
4099-001 PORTO
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Exmo.(a) Sr.(a)
Ana Rita Soares Marques
Rua Dr. Roberto Frias s/n
4200-465 Porto

ASSUNTO: Projeto de Investigação Trabalho Académico TA - Mestrado - **"Análise de pé diabético através de termografia médica normalizada e automatizada" - N/ REF.ª 2014.085(057-DEFI/083-CES)**

O Conselho de Administração do CHP **autoriza** a realização do estudo de investigação acima mencionado nesta Instituição, no(s) Serviço(s) de Endocrinologia, sendo Investigador(a) Principal, o(a) aluno(a) da Faculdade Engenharia UP, Ana Rita Soares Marques.
O estudo de investigação foi previamente analisado pela Comissão de Ética para a Saúde e pelo Gabinete Coordenador de Investigação do CHP, bem como pela Direção Clínica, tendo obtido Parecer Favorável.

Cumprimentos,

CONSELHO DE ADMINISTRAÇÃO
29 / 1 / 2014

Dr. SOLLARI ALLEGRO — Presidente
Dr.ª ÉLIA GOMES — Vogal Executiva
Dr. PAULO BARBOSA — Director Clínico
Dr. RUI PEDROSO — Vogal Executivo
Enf.ª EDUARDO ALVES — Enfermeiro Director

* Em todas as eventuais comunicações posteriores sobre este estudo é indispensável indicar a nossa ref.ª.

centro hospitalar do Porto

Hospital de Santo António Maternidade Júlio Dinis Hospital Maria Pia

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APRECIAÇÃO E PARECER PARA A REALIZAÇÃO DE **Ensaio Clínico TA - Mestrado**

Título: **"Análise de pé diabético através de termografia médica normalizada e automatizada"**		Ref.ª: **2014.085(057-DEFI/083-CES)**
Protocolo/Versão:		Investigador: **Ana Rita Soares Marques** **Faculdade Engenharia da UP**

DIRECÇÃO DE ENFERMAGEM:	**DIRECÇÃO CLÍNICA:**
☒ **NÃO SE APLICA**	☒ **PARECER FAVORÁVEL**
☐ **PARECER FAVORÁVEL**	☐ **PARECER NÃO FAVORÁVEL**
☐ **PARECER NÃO FAVORÁVEL**	
Data:	Data: 22/04/14

DR. PAULO BARBOSA
(Director Clínico)

Em conformidade. Pode ser autorizado

20/04/2014

Prof.ª Doutora Luísa Lobato
Diretora do DEFI

Prof.ª Doutora Luísa Lobato
Diretora do DEFI

centro hospitalar
do Porto

Hospital de Santo António Maternidade Júlio Dinis Hospital Maria Pia

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COMISSÃO DE ÉTICA PARA A SAÚDE

APRECIAÇÃO E VOTAÇÃO DO PARECER

Deliberação	Data: 7.5.2014	Órgão: Reunião Plenária

Título: **"Análise de pé diabético através de termografia médica normalizada e automatizada"**		Ref.ª: **2014.085(057-DEFI/083-CES)**
Protocolo/Versão:		Investigador: **Ana Rita Soares Marques** **Faculdade Engenharia da UP**

A Comissão de Ética para a Saúde – CES do CHP, ao abrigo do disposto no Decreto-Lei n.º 97/95, de 10 de Maio, em reunião realizada nesta data, apreciou a fundamentação do relator sobre o pedido de parecer para a realização de **Trabalho Académico - Mestrado** acima referenciado:

Ouvido o Relator, o processo foi votado pelos Membros da CES presentes:

Presidente: Dr.ª Luisa Bernardo
Vice-Presidente: Dr. Paulo Maia

Dr.ª Paulina Aguiar, Dr.ª Fernanda Manuela, Enf.ª Paula Duarte, Prof.ª Doutora Maria Manuel Araújo Jorge, Dr. Jorge Andrade da Silva

Resultado da votação:

PARECER FAVORÁVEL

A deliberação foi aprovada por unanimidade.

Pelo que se submete à consideração superior.

AUTORIZADO
Dr. Severo Torres
Adjunto do Diretor Clínico
Data: 22/5/2014

Data 7.5.2014

A Presidente da CES

Dr.ª Luisa Bernardo

APPENDIX B

U.PORTO
FEUP FACULDADE DE ENGENHARIA
UNIVERSIDADE DO PORTO

DEFI
DEPARTAMENTO DE ENSINO, FORMAÇÃO E INVESTIGAÇÃO
centro hospitalar do Porto

TERMO DE CONSENTIMENTO INFORMADO

Título do estudo de investigação: Diabetic foot thermophisiology characterization

Eu, abaixo-assinado (Nome completo do indivíduo participante do estudo):_____

Fui informado de que o Estudo de Investigação acima mencionado se destina a investigar a utilização da termografia médica na avaliação fisiológica tanto na identificação precoce, como na avaliação dos tratamentos aos doentes com pé diabético.
Sei que neste estudo está prevista a realização de um questionário e posterior recolha de imagens térmicas, tendo-me sido explicado em que consiste e quais os seus possíveis efeitos.

Foi-me garantido que todos os dados relativos à identificação dos Participantes neste estudo são confidenciais e que será mantido o anonimato.

Sei que posso recusar-me a participar ou interromper a qualquer momento a participação no estudo, sem nenhum tipo de penalização por este facto.

Compreendi a informação que me foi dada, tive oportunidade de fazer perguntas e as minhas dúvidas foram esclarecidas.

Aceito participar de livre vontade no estudo acima mencionado.

Também autorizo a divulgação dos resultados obtidos no meio científico, garantindo o anonimato.

Nome do Participante no estudo

Data	Assinatura
___/___/_____	_____

Nome do Investigador Responsável

Data	Assinatura
___/___/_____	_____

APPENDIX C

INQUÉRITO AOS VOLUNTÁRIOS

Data de realização do inquérito: __/__/_____

Género: ❑ Masculino ❑ Feminino ❑Outro

Data de nascimento: __/__/_____

Peso: _____ (kg)

Altura: _____ (m)

Lesões ou cirurgias realizadas nos últimos meses: ❑ Não ❑ Sim

Índice de glicose: _____

HISTÓRICO

1. Possui alguma destas condições crónicas?

❑ Diabetes tipo 1 ❑ Diabetes tipo 2 ❑ Diabetes gestacional

2. Possui uma máquina para medir o nível de açúcar no sangue (glucose)?

❑ Não ❑ Sim

3. Com que frequência faz o teste para medir o nível de açúcar no sangue?

❑ Quase nunca ❑ Frequentemente ❑Diariamente

MEDICAÇÃO

1. Na última semana tomou comprimidos para a diabetes?

❑ Não ❑ Sim ❑ Não sei

Especifique o(s) nome(s) dos comprimidos que tomou: _____

2. Na última semana tomou injecções de insulina?

❑ Não ❑ Sim ❑ Não sei

CONDIÇÃO DE SAÚDE

1. Em geral, como classifica a sua saúde:

❑ Muito Debilitada ❑ Debilitada ❑ Razoável ❑ Boa ❑ Excelente

2. Possui ou já possuiu alguma lesão nos pés devido à condição crónica (diabetes) que apresenta?

❑ Não ❑ Sim

Quais? (por exemplo, infecções na pele, fissuras, micoses)

_____

3. Apresenta falta de sensibilidade nos pés?

❑ Não ❑ Sim

Caso a resposta seja <u>afirmativa</u>, indique qual das seguintes opções melhor descreve melhor a sua situação.

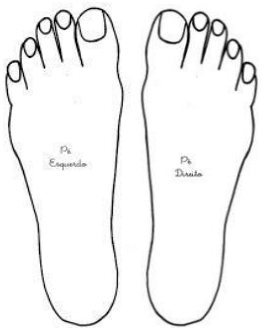
❑Falta de sensibilidade leve ❑Falta de sensibilidade moderada

❑ Falta de sensibilidade intensa

4. Já teve de amputar algum dedo do pé, devido a complicações resultantes de lesões, mais comumente denominadas de "pé diabético"?

❑ Não ❑ Sim

Se sim, assinale na figura qual dedo sofreu amputação:



5. Assinale para cada uma das seguintes questões, a resposta que melhor descreve o seu estado de saúde.

Mobilidade

Não tenho qualquer problema em relação à minha mobilidade ❑
Tenho alguns problemas em relação à minha mobilidade ❑
Tenho muitos problemas de mobilidade, e necessito de ajuda externa ❑

Cuidados pessoais

Não tenho qualquer problema para em realizar os meus cuidados pessoais ❑
Tenho algumas dificuldades ao vestir-me e com os cuidados de higiene ❑
Sou incapaz de vestir-me e ter cuidados de higiene sozinho ❑

Actividades diárias (por exemplo, trabalho, estudo, lides domésticas)

Não tenho qualquer problemas ao realizar estas actividades ❑
Tenho algumas dificuldades para realizar estas atividades ❑
Estou incapacitado de realizar estas atividades ❑

Dor/Desconforto

Não sinto qualquer dor ou desconforto ❑
Sinto alguma dor e desconforto ❑
Sinto dor e desconforto extremos ❑

6. Caso sinta dor ou desconforto assinale na escala seguinte, qual das seguintes opções descreve melhor a sua situação.

❑Dor ou desconforto leve ❑Dor ou desconforto moderado

❑ Dor ou desconforto intenso

CUIDADOS MÉDICOS

1. Quando visita o seu médico, com que frequência apresenta este tipo de questões (circule o número que melhor se adequa às suas respostas).

	Nunca	**Quase nunca**	**Às vezes**	**Muitas vezes**	**Sempre**
Prepara uma lista de questões/dúvidas para o seu médico	0	1	2	3	4

Faz questões sobre o seu tratamento ou dúvidas relacionados com o mesmo	0	1	2	3	4
Discute algum problema pessoal que pode estar relacionado com a sua doença	0	1	2	3	4

2. Nos últimos 6 meses, quantas vezes visitou o seu médico?
_____ vezes

3. Nos últimos 6 meses quantas vezes recorreu aos serviços de urgência do hospital?
_____ vezes

4. Nos últimos 6 meses, quantas vezes esteve hospitalizado (uma noite ou mais)?
_____ vezes

5. Quantas vezes o médico ou enfermeiro analisou os seus pés nos últimos 6 meses?
_____ vezes

QUALIDADE DE VIDA

1. Em relação à sua qualidade de vida, circule o número que melhor se adequa à sua situação.

	Nunca	**Quase nunca**	**Às vezes**	**Muitas vezes**	**Sempre**
Sente-se desencorajado/desanimado em relação ao seu problema de saúde	0	1	2	3	4
Tem medo em relação ao seu estado de saúde no futuro	0	1	2	3	4
A saúde é uma preocupação constante na sua vida	0	1	2	3	4

2. Para os doentes que possuem complicações graves derivadas da diabetes, como por exemplo, pé diabético, qual a sua opinião em relação à necessidade de implementar novos métodos de detecção e diagnóstico que não sejam dolorosos e invasivos para o paciente?

❑ Discordo ❑ Indiferente ❑ Concordo ❑ Acho extremamente importante

Obrigado pela sua atenção!

APPENDIX D

PROTOCOLO DE TERMOGRAFIA

Este protocolo é baseado no "*Glamorgan Protocol*", uma referência para os procedimentos padrão recomendados para a recolha e avaliação de imagens térmicas em aplicações médicas.

1. Localização para a recolha de imagens térmicas
Sala de exames

- Deve ser mantida uma distância mínima entre a câmara termográfica e o voluntário – normalmente 1 metro. A sala deve ter, no mínimo, 2x3 metros.
- A sala deve conter apenas o material necessário para a recolha de imagens, de forma a evitar reflexões térmicas e criar artefactos nas imagens.

Ambiente controlado

- A sala deve ser mantida a uma temperatura constante entre 18-24°C, normalmente 22±1°C, e será necessário que antes de iniciar a captura das imagens, que o voluntário permaneça na sala durante 15 minutos para que o seu corpo se mantenha em equilíbrio com a temperatura da sala.
- Radiação ultravioleta deve ser evitada. Todas as janelas e portas devem ser devidamente fechadas.
- A humidade relativa deve ser inferior a 50%.
- A sala deve conter um equipamento de ar condicionado, de forma a manter a temperatura recomendada constante. O fluxo de ar proveniente do equipamento não deve ser orientado para o paciente.
- O equipamento deve ser mantido fora da zona do voluntário, de modo a evitar perturbações.
- Deve existir um cubículo mínimo na sala de exame, com as mesmas condições ambientais, para que o voluntário possa retirar/vestir as roupas com privacidade e descansar durante o período de aclimatização.
- Não deve haver luz directamente incidida no voluntário, para evitar reflexões térmicas.

2. Equipamento necessário
O equipamento necessário para a recolha de dados será:

- Câmara *FLIR A325*, para a captura das imagens de termografia. Esta câmara termográfica tem uma resolução real integrada de 320 x 240 *pixels* , a qual possui sensores que permite medir as temperaturas que variam entre -20°C a +120°C. Apresenta sensibilidade para detectar diferenças de temperatura menores que 0,08°C e possui exatidão de ± 2°C da temperatura absoluta.

- Oxímetro de pulso digital 50H – versão 1.0 (Micter®), dispositivo médico que mede indiretamente a quantidade de oxigénio no sangue de um paciente.

- Tripé, para instalar e posicionar a câmara e ao nível dos pacientes.

- *FLIR Researcher Pro 2.10*, software de análise de imagens infravermelhos.

3. Cuidados para o equipamento termográfico

- A câmara termográfica deve ser ligada 40 minutos antes da captura de imagens.
- O equipamento deve garantir um foco automático ou manual.
- É recomendado o uso da temperatura externa como referência para a calibração, de modo a garantir a qualidade da imagem e sensibilidade da câmara.
- O tipo de lentes da câmara deve ser considerado. Lentes com ângulos mais abertos reduzem a distância entre a câmara e o sujeito, mas ao mesmo tempo aumentam a distorção periférica da imagem.
- O tripé para suporte da câmara deve evitar ângulos obtusos.
- Cada imagem, ou conjunto de imagens deve indicar a gama de temperatura usada e o respectivo código de cor/ escala de temperaturas. A escala e gama de cores, comummente utilizado em aplicações médicas, varia entre 25°C e 37°C.
- As temperaturas do fundo que podem diminuir a intensidade da imagem devem ser evitadas. As respectivas cores devem ser substituídas por branco, preto ou cinzento, de forma a conseguir uma melhor apresentação visual.

4. Sujeito/Voluntário

Informação para o voluntário

O voluntário deve ser informado para:

- Evitar o uso de aplicações tópicas: como o uso de ornamentos e maquilhagem no dia do exames.
- Evitar grandes refeições e ingestão de café ou chá duas horas antes do exame.
- Não fumar durante duas horas antes do exame.
- Evitar o uso de roupas muito justas e apertadas.
- Evitar a prática de exercício físico incluindo métodos de fisioterapia, como: electroterapia, ultra-sons, tratamento com calor, crioterapia, massagens e hidroterapia, nas últimas 6 horas antes do exame.
- Evitar a ingestão de medicamentos, nomeadamente: esteróides, bloqueadores do sistema nervoso autónomo e medicações vasoactivas, opiáceos e autocolantes dérmicos, pelo menos 24 horas antes do exame. Excepções devem ser anotadas.

Preparação pré-recolha

- O voluntário deve ser informado sobre os procedimentos do exame, antes do seu início.
- O voluntário deve ser instruído para retirar a roupa e os ornamentos.
- O voluntário deve ser informado para sentar-se ou descansar na sala de exames no período de aclimatização. O período mínimo é de 10 minutos.

- O voluntário deve evitar contacto entre as partes do corpo, como dobrar ou cruzar braços e pernas.
- Em casos de avaliação térmica dos membros inferiores, deve ser usado um apoio de forma a evitar o contacto direto com o chão.

Posições para a recolha das imagens

- O voluntário deve assumir posições corretas, de forma a serem adquiridas vistas padrão de regiões do corpo.
- Alguma comparação/conclusão obtida em diferentes condições deve ser evitada.

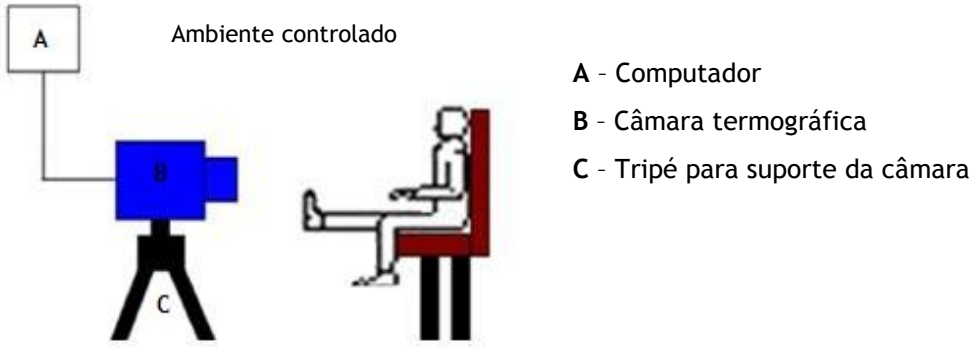


Figura 1 - Ilustração do posicionamento material necessário para a captura das imagens termográficas. A temperatura e a humidade da sala deve ser mantida dentro de um limite confortável, e a câmara deverá ser colocada perpendicular à superfície de observação para minimizar erros geométricos na medição da temperatura.

Campo de visão

- O voluntário deve conservar a distância mínima à câmara estabelecida, para que o campo de visão varie o mínimo possível. O tamanho da imagem está dependente desta distância e da distância focal da lente da câmara.

APPENDIX E

Table - Appendix A - Mann Whitney U, Wilcoxon W Z and significancy of Mann Whitney test for ANS ROIs temperatures in 2nd stage

ROIs of ANS	U	W	Z	p
N1L	66.00	886.00	-4.23	0.00
N1R	43.50	863.50	-4.67	0.00
N1S	139.00	959.00	-2.80	0.01
N2L	62.50	882.50	-4.30	0.00
N2R	43.50	863.50	-4.67	0.00
N2S	100.50	920.50	-3.56	0.00
N3L	56.00	876.00	-4.43	0.00
N3R	53.50	873.50	-4.47	0.00
N3S	136.50	956.50	-2.85	0.00
N4+5L	45.50	865.50	-4.63	0.00
N4+5R	35.00	855.00	-4.84	0.00
N4+5S	51.50	871.50	-4.52	0.00
N6L	73.50	893.50	-4.08	0.00
N6R	50.00	870.00	-4.54	0.00
N6S	99.50	919.50	-3.59	0.00

Table - Appendix B - Mann Whitney U, Wilcoxon W Z and significancy of Mann Whitney test for VS ROIs temperatures in 2nd stage

ROIs of VS	U	W	Z	p
V1L	24.00	844.00	-5.06	0.00
V1R	25.00	845.00	-5.04	0.00
V1S	106.00	926.00	-3.46	0.00
V2L	49.50	869.50	-4.55	0.00
V2R	7.50	827.50	-5.38	0.00
V2S	56.50	876.50	-4.44	0.00
V3L	10.00	830.00	-5.33	0.00
V3R	5.50	825.50	-5.42	0.00
V3S	55.50	875.50	-4.47	0.00
V4L	10.50	830.50	-5.32	0.00
V4R	9.00	829.00	-5.35	0.00
V4S	80.00	900.00	-3.98	0.00
V5L	16.50	836.50	-5.20	0.00
V5R	16.00	836.00	-5.21	0.00
V5S	113.50	933.50	-3.31	0.00
V6L	54.50	874.50	-4.45	0.00
V6R	37.00	857.00	-4.80	0.00
V6S	103.50	923.50	-3.50	0.00
V7L	72.00	892.00	-4.11	0.00
V7R	45.00	865.00	-4.64	0.00
V7S	88.50	908.50	-3.81	0.00
V8L	73.00	893.00	-4.09	0.00
V8R	51.50	871.50	-4.51	0.00
V8S	80.00	900.00	-3.97	0.00
V9L	47.00	867.00	-4.60	0.00
V9R	47.00	867.00	-4.60	0.00
V9S	128.00	948.00	-3.02	0.00

APPENDIX F

Table - Appendix C- *Mann Whitney U, Wilcoxon W Z and significancy of Mann Whitney test for ANS ROIs temperatures in 3rd stage*

ROIs of ANS	U	W	Z	p
N1L	74.00	894.00	-4.07	0.00
N1R	34.00	854.00	-4.86	0.00
N1S	118.50	938.50	-3.20	0.00
N2L	62.50	882.50	-4.30	0.00
N2R	36.50	856.50	-4.81	0.00
N2S	77.00	897.00	-4.02	0.00
N3L	47.50	867.50	-4.59	0.00
N3R	46.00	866.00	-4.62	0.00
N3S	141.50	961.50	-2.75	0.01
N4+5L	51.00	871.00	-4.52	0.00
N4+5R	47.50	867.50	-4.59	0.00
N4+5S	92.50	912.50	-3.71	0.00
N6L	77.50	897.50	-4.00	0.00
N6R	51.00	871.00	-4.52	0.00
N6S	59.50	879.50	-4.39	0.00

Table - Appendix D- Mann Whitney U, Wilcoxon W Z and significancy of Mann Whitney test for VS ROIs temperatures in 3rd stage

ROIs of VS	U	W	Z	p
V1L	44.50	864.50	-4.65	0.00
V1R	57.50	877.50	-4.39	0.00
V1S	160.50	980.50	-2.37	0.02
V2L	55.50	875.50	-4.43	0.00
V2R	24.50	844.50	-5.04	0.00
V2S	86.00	906.00	-3.86	0.00
V3L	16.50	836.50	-5.20	0.00
V3R	19.00	839.00	-5.15	0.00
V3S	101.00	921.00	-3.56	0.00
V4L	22.50	842.50	-5.09	0.00
V4R	23.00	843.00	-5.08	0.00
V4S	53.50	873.50	-4.50	0.00
V5L	31.50	851.50	-4.91	0.00
V5R	28.00	848.00	-4.98	0.00
V5S	142.50	962.50	-2.73	0.01
V6L	56.50	876.50	-4.41	0.00
V6R	46.00	866.00	-4.62	0.00
V6S	107.00	927.00	-3.43	0.00
V7L	77.50	897.50	-4.00	0.00
V7R	52.00	872.00	-4.50	0.00
V7S	109.00	929.00	-3.40	0.00
V8L	77.50	897.50	-4.00	0.00
V8R	56.00	876.00	-4.42	0.00
V8S	80.50	900.50	-3.95	0.00
V9L	48.00	868.00	-4.58	0.00
V9R	44.50	864.50	-4.65	0.00
V9S	153.50	973.50	-2.51	0.01

APPENDIX G

Table - Appendix E- Mann Whitney U, Wilcoxon W Z and significancy of Mann Whitney test for ANS ROIs temperatures of partipants with neuropathic and neuroischaemic ulcers.

ROIs of ANS	U	W	Z	p
N1L	226.00	691.00	-0.94	0.35
N1R	246.00	417.00	-0.51	0.61
N1S	240.50	705.50	-0.63	0.53
N2L	231.50	696.50	-0.82	0.41
N2R	236.00	407.00	-0.72	0.47
N2S	234.50	699.50	-0.76	0.45
N3L	248.00	713.00	-0.47	0.64
N3R	250.50	421.50	-0.42	0.68
N3S	202.50	667.50	-1.44	0.15
N4+5L	222.00	687.00	-1.02	0.31
N4+5R	215.00	386.00	-1.17	0.24
N4+5S	179.00	644.00	-1.94	0.05
N6L	219.50	684.50	-1.08	0.28
N6R	234.00	405.00	-0.77	0.44
N6S	205.00	670.00	-1.39	0.17

Table - Appendix F- Mann Whitney U, Wilcoxon W Z and significancy of Mann Whitney test for VS ROIs temperatures of partipants with neuropathic and neuroischaemic ulcers.

ROIs of VS	U	W	Z	p
V1L	243.50	708.50	-0.56	0.57
V1R	224.00	395.00	-0.98	0.33
V1S	215.50	680.50	-1.16	0.25
V2L	239.50	704.50	-0.65	0.52
V2R	230.50	401.50	-0.84	0.40
V2S	176.50	641.50	-1.99	0.05
V3L	260.50	725.50	-0.20	0.84
V3R	265.50	436.50	-0.10	0.92
V3S	236.50	701.50	-0.71	0.48
V4L	258.50	723.50	-0.25	0.81
V4R	254.50	425.50	-0.33	0.74
V4S	186.50	651.50	-1.78	0.08
V5L	265.00	730.00	-0.11	0.92
V5R	258.00	429.00	-0.26	0.80
V5S	201.50	666.50	-1.46	0.14
V6L	247.00	712.00	-0.49	0.62
V6R	255.50	426.50	-0.31	0.76
V6S	195.50	660.50	-1.59	0.11
V7L	231.50	696.50	-0.82	0.41
V7R	251.50	422.50	-0.39	0.69
V7S	213.00	678.00	-1.22	0.22
V8L	222.00	687.00	-1.02	0.31
V8R	239.50	410.50	-0.65	0.52
V8S	243.00	414.00	-0.58	0.57
V9L	241.50	706.50	-0.61	0.54
V9R	253.00	424.00	-0.36	0.72
V9S	213.50	678.50	-1.21	0.23

APPENDIX H

Table - Appendix G- Mann Whitney U, Wilcoxon W Z and significancy of Mann Whitney test for ANS ROIs temperatures of partipants with ischaemic and neuroischaemic ulcers.

ROIs of ANS	U	W	Z	p
N1L	17.00	20.00	-0.13	0.90
N1R	17.50	188.50	-0.06	0.95
N1S	16.00	19.00	-0.25	0.80
N2L	14.50	17.50	-0.44	0.66
N2R	14.00	185.00	-0.50	0.61
N2S	14.00	185.00	-0.51	0.61
N3L	17.50	188.50	-0.06	0.95
N3R	15.50	18.50	-0.32	0.75
N3S	15.50	186.50	-0.32	0.75
N4+5L	13.00	16.00	-0.63	0.53
N4+5R	15.00	186.00	-0.38	0.71
N4+5S	12.50	183.50	-0.69	0.49
N6L	13.50	16.50	-0.57	0.57
N6R	16.50	187.50	-0.19	0.85
N6S	14.00	17.00	-0.51	0.61

Table - Appendix H- Mann Whitney U, Wilcoxon W Z and significancy of Mann Whitney test for VS ROIs temperatures of partipants with ischaemic and neuroischaemic ulcers.

ROIs of VS	U	W	Z	p
V1L	10.00	13.00	-1.01	0.31
V1R	16.00	187.00	-0.25	0.80
V1S	17.00	20.00	-0.13	0.90
V2L	12.00	15.00	-0.76	0.45
V2R	17.00	20.00	-0.13	0.90
V2S	15.00	18.00	-0.38	0.71
V3L	8.00	11.00	-1.26	0.21
V3R	17.00	188.00	-0.13	0.90
V3S	10.00	181.00	-1.01	0.31
V4L	5.00	8.00	-1.64	0.10
V4R	13.00	184.00	-0.63	0.53
V4S	6.00	177.00	-1.51	0.13
V5L	11.00	14.00	-0.88	0.38
V5R	16.50	19.50	-0.19	0.85
V5S	15.00	18.00	-0.38	0.71
V6L	13.00	16.00	-0.63	0.53
V6R	12.00	183.00	-0.76	0.45
V6S	7.50	178.50	-1.33	0.19
V7L	12.50	15.50	-0.69	0.49
V7R	15.50	18.50	-0.32	0.75
V7S	15.00	18.00	-0.38	0.71
V8L	16.50	19.50	-0.19	0.85
V8R	14.00	185.00	-0.51	0.61
V8S	16.00	187.00	-0.25	0.80
V9L	16.50	187.50	-0.19	0.85
V9R	14.50	17.50	-0.44	0.66
V9S	15.00	186.00	-0.38	0.71