The Application of Thermography as a Screening Tool to Detect Type 2 Diabetic Foot Disease.

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Abstract

Aim:

To determine whether thermography can be used as a screening modality to detect T2DM complications by measuring the cutaneous temperature of specific areas of the foot and using the logistic regression curves and equations provided in literature.

Method and Methodology:

This was a quantitative, postpositivist and non-experimental correlational research to investigate the sensitivity, specificity, positive-predictive value (PPV) and negative predictive value (NPV) of thermography in identifying diabetic foot complications in participants with Type 2 Diabetes Mellitus. For each participant, a thermogram of the plantar aspect of the foot was taken using FLIR T630. FLIR ResearchIR programme generated the cutaneous temperature on eight regions of interest (ROIs). The probability of complications for each foot was calculated using equations previously published in literature based on the cutaneous temperature. Another podiatrist, blinded to the results of the thermography analysis, performed Ankle-Brachial Pressure Index, Spectral Doppler Waveform Analysis (for detection of peripheral arterial disease), and 10g Monofilament and 128Hz Tuning Fork to diagnose neuropathy or neuroischaemia. The probability of diabetic foot complications was then compared with the actual presence or absence of diabetic foot complications. The sensitivity, specificity, positive-predictive and negative predictive values were calculated for four different probability cut-off points (0.4, 0.5, 0.6, 0.7) on eight different regions of interest.

Results:

Using a 0.5 probability cut-off point, it was found that the sensitivity of detecting complications was high, ranging from 93% to 97% in the toes and 93% to 100% in the forefoot. However, specificity was lower, ranging from 54% to 69% in the forefoot and 69% to 80% in the toes. The positive predictive value varied from 0.71 to 0.79 in the toes and from 0.64 to 0.71 in the forefoot, while the negative predictive value ranged from 0.92 to 0.96 in the toes and 0.92 to 1 in the forefoot. Increasing the probability cut-off point yielded higher specificity and PPV but lower sensitivity and NPV. Importantly, all participants with PAD, neuropathy, and neuroischemia were identified using the 1st MTH ROI.

Conclusion:

Results indicate that thermography can effectively detect chronic diabetic foot complications with high sensitivity and specificity. In a clinical setting, this technology can be a helpful tool for reducing waiting times and resources for diabetic foot screening and detecting T2DM foot complications faster and more conveniently.

Keywords: Thermography, Thermal Camera, Type 2 Diabetes, Diabetic Foot Complications, Peripheral Arterial Disease, Neuropathy, Neuroischaemia

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DECLARATIONS BY POSTGRADUATE STUDENTS

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I hereby declare that I am the legitimate author of this Dissertation and that it is my original work.

No portion of this work has been submitted in support of an application for another degree or qualification of this or any other university or institution of higher education.

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I declare that I have abided by the University's Research Ethics Review Procedures. Research Ethics & Data Protection form code V_11022020 5098.

As a Master's student, as per Regulation 77 of the General Regulations for University Postgraduate Awards 2021, I accept that should my dissertation be awarded a Grade A, it will be made publicly available on the University of Malta Institutional Repository.

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Chapter 1 : Introduction

Background

Type 2 Diabetes (T2DM) is a metabolic disorder causing high plasma glucose levels due to problems with insulin sensitivity, insulin production, and functionality of beta cells within the pancreas (Robertson, 1995, Mealey and Ocampo, 2007). It is estimated that 462 million people worldwide are living with T2DM, which accounts for around 6.28% of the world's population (Khan et al., 2020). This is expected to increase to around 700 million by 2045 (Rossboth et al., 2020). According to Cuschieri (2020) around 10.31% of 18–70-year-olds in Malta are living with T2DM. If the plasma glucose level is uncontrolled for a long time, several complications around the body may occur. Such complications may include cardiovascular disease, stroke, retinopathy, nephropathy, dental disease, reduced infection resistance, and diabetic foot complications (Papatheodorou et al., 2018). The American Diabetes Association (2018) reports that the economic burden of diabetes has surged by 26% between 2012 and 2017. This can be attributed to the higher incidence rate of diabetes and increased expenditure per diabetic patient. It highlights the criticality of timely identification and management of T2DM to avert subsequent complications.

As the number of patients with T2DM rises globally, so does the incidence of diabetic foot complications. The primary complications include peripheral arterial disease (PAD), neuropathy, and a combination of both called neuroischemia. These complications may further give rise to infections and even amputations. During the disease, around 25% of all patients with diabetes develop foot complications (Singh et al., 2005).

It is a common occurrence for patients with T2DM to have peripheral vascular disease, as reported by Formosa, Gatt, and Chockalingam in 2012. In fact, PAD is twice as prevalent in individuals with diabetes compared to those who are not affected by the condition (Selvin and Erlinger, 2004). PAD is the term used to describe the narrowing and obstruction of blood flow in the peripheral arteries. In the early stages of PAD, it often does not exhibit any symptoms, which can make it challenging to diagnose (Hirsch et al., 2001). The high plasma glucose level in patients with diabetes aids in the formation of advanced glycation end products, which participate in vascular damage (De Vos et al., 2013). Atherosclerosis in T2DM commonly

occurs in the arteries below the knee, such as the posterior tibial artery, peroneal arteries, and popliteal artery (Jude et al., 2001). HbA1c refers to glycosylated haemoglobin and indicates the blood glucose level in the previous three months (Rawal et al., 2016). The higher the HbA1c, the higher the risk of developing diabetes-related complications. In fact, when the HbA1c is higher than 7.5%, it is five times more likely that PAD-associated hospitalization occurs when compared to individuals with good glycemic control (Selvin et al., 2006).

Peripheral neuropathy is another complication of T2DM that can affect the foot. This condition can have a negative impact on one's quality of life, as it can interfere with daily activities (Ko & Cha, 2012). 50 % of patients with diabetes experience neuropathy during their lifetime, the most common type being distal symmetrical polyneuropathy (Hicks et al., 2019). Oxidative stress and inflammation leading to cell death and nerve dysfunction are thought to be the reasons behind neuropathy (Fedelman et al., 2017). Diabetic peripheral neuropathy often goes unreported and left untreated (Daousi et al., 2004). Neuroischaemia occurs when both neuropathy and PAD are present at the same time. This tends to be more challenging to treat and portends a higher risk of developing infection, amputation and even death (Ndip & Jude et al., 2009).

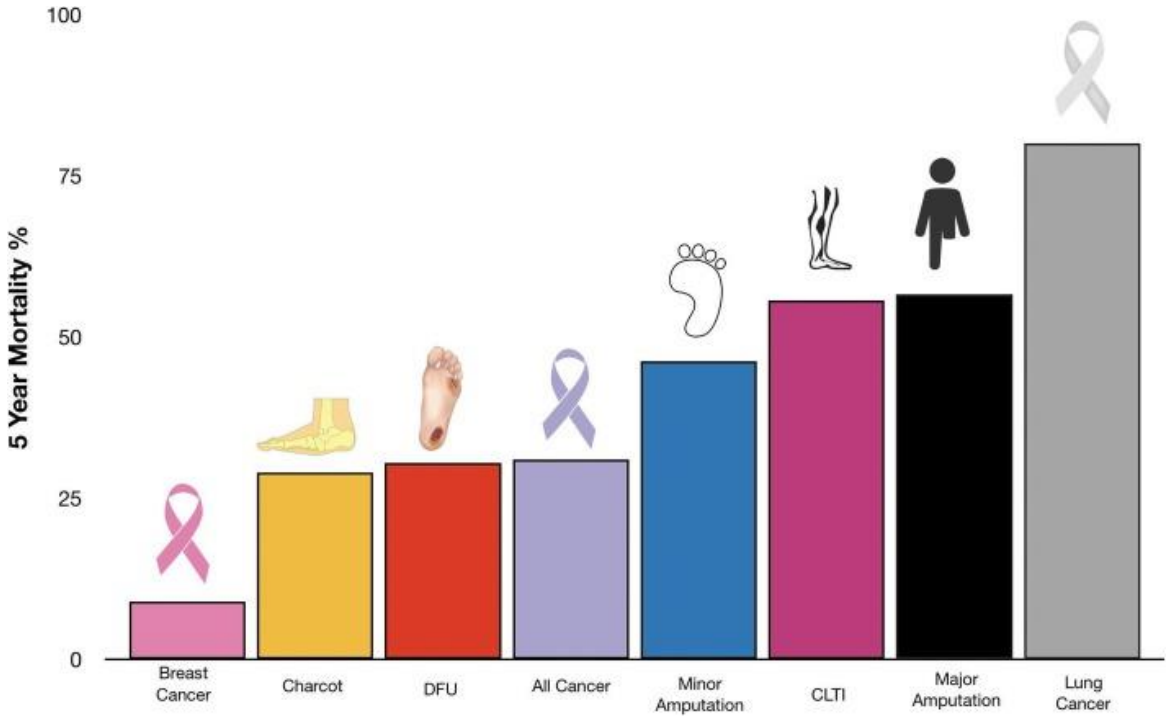

Figure 1.1: Five-year mortality rates (Retrieved from Armstrong et al. (2020)

Armstrong et al. (2020) reported that the 5-year mortality rates for diabetic foot complications, including Charcot foot, diabetic foot ulcer, minor amputation, and major amputation, are as high as 29%, 30.5%, 46.2%, and 56.6%, respectively. These rates are alarming, particularly when compared to the 5-year mortality rate for all cancer types, which is 31% on average (varying from 9% in breast cancer to 80% in lung cancer) (Armstrong et al., 2020).

It is crucial to undergo regular foot screening to diagnose and treat T2DM foot complications at an early stage, thus reducing the risk of amputations. Formosa et al. (2013) recommend using ABPI and Doppler waveform to screen for PAD. ABPI is often used to detect PAD, but it can be challenging to compress the arterial wall in the presence of arterial calcification, which can result in misinterpretation of the severity of PAD (Raines et al., 1976). The hand-held Doppler is a useful tool to exclude the presence of PAD in patients with and without diabetes (Alavi et al., 2015), with the visual Doppler waveform interpretation found to be more reliable than audible Doppler waveform interpretation (Tehan & Chuter, 2015). Furthermore, high interrater reliability of visual spectral Doppler waveform interpretation among five experienced clinicians was found by Formosa et al. (2018). Screening for diabetic peripheral neuropathy commonly involves monofilament and vibration perception tests (Papatheodorou et al., 2018). Wang et al. (2017) found that although monofilament testing has acceptable levels of specificity, it is not sensitive enough to provide true positive results.

According to the American Diabetes Association (2018), individuals with diabetes should undergo a thorough foot evaluation once a year. However, identifying diabetic peripheral neuropathy and PAD can be a difficult and time-consuming task as different methods such as ABPI, Doppler, 10g monofilament, and 128Hz tuning fork are used. In fact, conducting an ABPI evaluation alone could take up to 15 minutes (McClary & Massey, 2023), placing pressure on clinicians to perform a diabetic foot screening in time. Despite the efforts made to conduct regular foot examinations, both prevention and early detection methods must be improved (Boulton et al., 2005; Boyko et al., 2006).

Advancements in research have enhanced our comprehension of diabetic foot complications, and the exploration of new and innovative technologies may equip medical professionals with the ability to offer effective interventions to prevent and treat such complications. One such technology is the use of infrared thermographic cameras, which can detect temperature changes in the foot. These cameras are capable of measuring surface temperature by detecting infrared

radiation without requiring direct contact (Speakman, 1998). PAD and neuropathy influence the cutaneous temperature of the plantar aspect of the foot (Bagavathiappan et al., 2010; Gatt et al., 2018). Changes in foot temperature can be detected by manual palpation; however, these changes may be too subtle and remain undetected. According to Sun et al. (2006), an increase in temperature may be present up to a week before an ulcer appears, and therefore it is of utmost importance that these changes are detected as early as possible.

Thermography can detect subtle temperature changes in the foot that may indicate early signs of foot complications, such as inflammation, infection, neuropathy, or ischemia. An objective assessment of foot temperature that is not dependent on the subjective interpretation of the healthcare provider can be obtained using thermography. By detecting these temperature changes early, healthcare providers can take prompt action to prevent the progression of complications (Gatt et al., 2018; Ilo et al., 2020; Van Netten et al.,2014).

This technique has already been used within the healthcare setting to detect complications in the breast, skin, Reynaud`s phenomenon and ulcerations (Lahiri et al., 2012, Otsuka et al., 2002, Wang et al., 2004). Thermography is considered safe since it is a non-contact and non-irradiate tool (Gatt et al., 2018). Furthermore, thermography is a cost-effective imaging technique compared to other imaging modalities, such as MRI or CT scans (Hernandez-Contreras et al., 2017). Studies have shown that monitoring skin temperature can lower the risk of ulceration in diabetic patients. Thermal imaging is an excellent method of quantifying skin temperature and can serve as an alternative means of detecting significant foot complications (Armstrong et al., 2007).

In 2018, Gatt et al. conducted a study to assess the effectiveness of thermography as a tool for detecting foot complications in individuals with T2DM. The study revealed that there was no significant difference in the average cutaneous foot temperature between healthy individuals and those with T2DM who did not have foot complications. No significant temperature differences were found between subjects with different foot complications of PAD, neuropathy and neuroischaemia. However, subjects with these T2DM foot complications were found to have significantly higher cutaneous foot temperatures than healthy subjects and subjects with T2DM but without foot complications. Furthermore, a logistic regression model created in this study showed that the higher the temperature, the higher the probability that foot complications are present and vice versa.

Results from the study performed by Gatt et al. (2018) indicate that if an increase in temperature in a diabetic foot is detected, the higher the probability that foot complications (PAD, neuropathy or neuroischaemia) are present. Furthermore, separate equations for the toes and forefoot cutaneous temperatures were generated to determine the probability of presence of T2DM. In this formula, *p* is the probability that a T2DM complications are present, and *1-p* is the probability that the patient is healthy.

$$\log_e\left(\frac{p}{1-p}\right) = -5.786 + 0.220 \ \text{temperature},$$

Figure 1.2: Logistic regression equation relating to toes. Retrieved from Gatt et al., 2018.

$$\log_e\left(\frac{p}{1-p}\right) = -6.949 + 0.254 \ \text{temperature},$$

Figure 1.3: Logistic regression equation relating to forefoot. Retrieved from Gatt et al., 2018.

Justification of the Study

Previous studies have already shown that there is an increase in cutaneous temperature when diabetic foot complications are present (Gatt et al., 2018; Bagavathiappan et al., 2010; Papanas et al., 2008; Carabott et al., 2019). The exact reason for this phenomenon is still unclear, but it is believed to be caused by PAD and neuropathy, which affect the feet's thermoregulatory mechanisms. Local ischemia can disrupt the noradrenergic vasoconstriction that is mediated by the sympathetic nervous system, leading to more blood flow to the skin's surface vessels instead of the deeper vessels. This results in warmer skin temperatures (Gatt et al., 2018).

Given the extensive number of patients living with T2DM worldwide, including in Malta, there is a clear need for a new screening method to allow for timely diabetic foot screening. Through this study, it may be proven that the thermal camera is a cost-effective, efficient, and secure

method to identify potential foot complications in patients with T2DM. Once a thermogram of the foot is taken and the temperature is extracted, the probability of T2DM foot complications will be determined. Individuals with a high likelihood of foot complications will receive a referral for additional testing. Should this be proven, it has the potential to significantly decrease the waiting time for diabetic foot screening, while also lessening the workload of clinicians.

This study will build on the work done by Gatt et al. (2018) and try to determine whether thermography can be used to detect T2DM foot complications. This will be done by measuring the foot cutaneous temperatures using a thermographic camera. The probability that T2DM complications are present will be extracted using the formulas from the logistic regression model. Medically validated tests to confirm or exclude the presence of T2DM complications include Doppler waveform, ABPI, 10g monofilament, and vibration testing using a 128Hz tuning fork. The prediction of foot complications will be compared to the results from medically validated tests to produce the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) to identify T2DM foot complications. Different probability cut-off points will be investigated (0.4, 0.5, 0.6, 0.7) to determine which one is the most effective when screening the diabetic foot.

Research Question

Can thermography be used as a screening modality to identify T2DM complications by measuring the cutaneous temperature of the foot?

Aim

This research aims to determine whether thermography can be used as a screening modality to identify T2DM foot complications by calculating its sensitivity, specificity, PPV and NPV.

Objectives

1. To record the plantar cutaneous temperatures of the foot using a thermographic camera.
2. Using the collected thermographic data, to determine the likelihood of complications related to T2DM.
3. To analyse if there is any statistical significance in the cutaneous foot temperatures between healthy feet and those with T2DM complications.
4. To investigate the potential use of the plantar cutaneous temperature of the foot in identifying foot complications associated with T2DM.
5. To investigate the probability cut-off point that provides the optimal sensitivity and specificity.

Layout of the Dissertation

This dissertation is divided into 6 chapters.

Chapter 1: This chapter will introduce the research conducted. This includes the background to T2DM foot complications, thermography, and justification for why this research is important. The research question, aim and objectives of this research are also included.

Chapter 2: Following the introduction in Chapter 1, this dissertation will include a literature review chapter that will take a detailed look at several studies and articles on T2DM foot complications and thermography to provide the latest research and aid in better understanding the need for this research to take place. Several keywords will be used, such as T2DM, PAD, neuropathy, neuroischaemia, Doppler US, ABPI, 10g monofilament, vibration sensation testing, thermography, thermographic camera, and thermal imaging.

Chapter 3: The methodology and method will be given with all the details in Chapter 3. This will include study design, recruitment of patients, inclusion and exclusion criteria, data collection and acquisition of thermal data.

Chapter 4: This chapter will contain all this research's results and statistical analysis. This will include anthropometric measurements and statistical analysis that will determine the specificity and sensitivity of thermography in detecting T2DM foot complications.

Chapter 5: Following the statistical analysis, a discussion will be formulated in Chapter 5. This will be based on the results obtained and how it compares to previous research and identify any suggestions for future research.

Chapter 6: This dissertation will end with the conclusion in chapter 6, containing closing remarks and notable points identified in chapters 4 and 5.

Chapter 2 : Literature Review

Literature Search

For this dissertation, an extensive literature review was carried out. Several electronic search engines were used to write this broad literature search including Google Scholar, Elsevier, Medline, World Journal of Diabetes, Diabetes Care, International Journal of Diabetes Mellitus, Pubmed, Journal of Internal Medicine, Science Direct, Journal of the American Podiatric Medical Association, National Statistics Office (NSO), and EUROSTAT. The European Heart Journal, Biomed Central, Malta, Medical Journal, the British Medical Journal, Middle European Journal of Medicine, American, Journal of Epidemiology, European Heart Network, Canadian Journal of Cardiology, Quality in Primary Care, American Diabetes Association, Diabetes and Primary Care were also used.

When conducting evidence-based research, it is useful to utilize the PICO process. This technique involves framing and answering a clinical question regarding a specific patient's problem, which helps to identify clinically relevant evidence in the literature. The acronym PICO stands for Patient/Population/Problem, Intervention/Indicator, Comparison/Control, and Outcome (Roever, 2018). The PICO model can help to create a strong research question by breaking it down into searchable elements and identifying relevant search terms (Palaskar, 2017). This research focuses on the T2DM population and the effectiveness of thermography as an intervention. It will be compared with medically validated tests that identify T2DM foot complications. The outcome will measure thermography's sensitivity, specificity, negative predictive value, and positive predictive value in identifying T2DM foot complications.

Support for this approach can be found in the literature that contains information related to Peripheral Arterial Disease, Type 2 Diabetes Mellitus, Neuropathy, Thermography, 10g Monofilament, Tuning fork, risk factors for Peripheral Arterial Disease, Toe Brachial Pressure Index, epidemiology of Type 2 Diabetes Mellitus, Ankle Brachial Pressure Index, Doppler Ultrasound and Diabetes in Malta. Other literature to support this research was accessed from medical textbooks containing information related to T2DM, thermography, PAD, neuropathy, neuroischaemia and medically validated tests to diagnose these diseases.

Type 2 Diabetes Mellitus

Healthy individuals maintain glucose homeostasis through their tissue's sensitivity to insulin and insulin secretion mechanisms, despite fluctuations in supply and demand (Kesavadev et al., 2019). However, T2DM is a chronic metabolic disorder that causes high levels of plasma glucose due to decreased insulin sensitivity and production, as well as a decrease in the functionality of Beta cells within the pancreas (Robertson, 1995; Mealey and Ocampo, 2007). As a result, less glucose is transported to the liver and muscles and fat cells leading to hyperglycaemia. Other factors contributing to elevated glucose levels include accelerated lipolysis by adipocytes, hyperglucagonemia by the alpha cells of the pancreas, increased glucose reabsorption in the kidneys, and central appetite dysregulation in the brain (Kesavadev et al., 2019). Elevated plasma and tissue glucose levels are toxic to the vascular endothelium and countless other vital organs (Kesavadev et al., 2019).

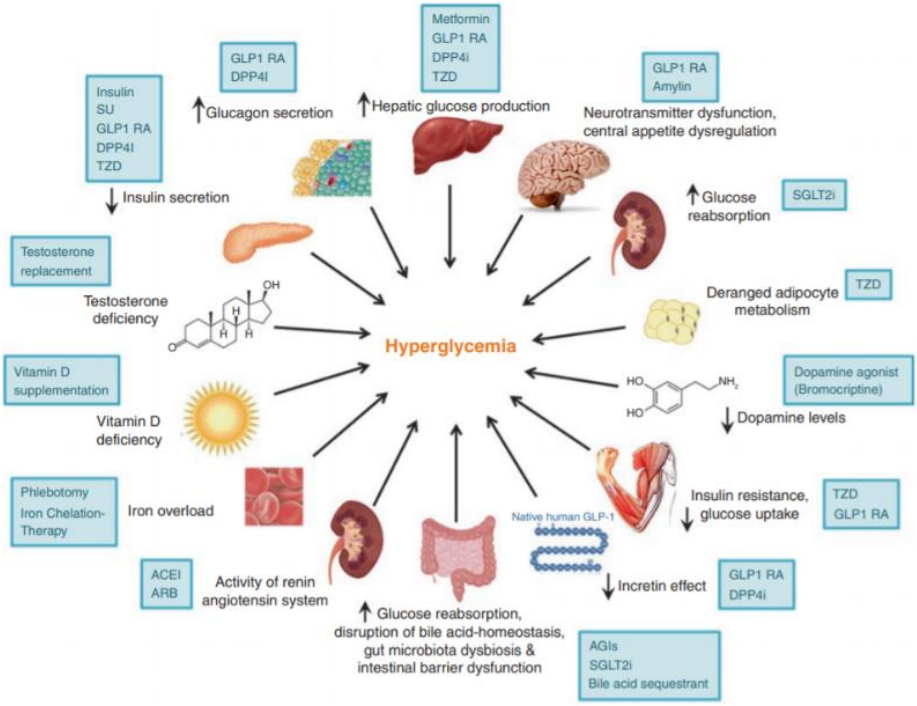

Figure 2.1: Causes of hyperglycaemia. retrieved from Kesavadev et al. (2019)

T2DM is thought to result from a combination of genetic, behavioural, and environmental risk factors (Zimmet, Alberti and Shaw, 2001). It is considered an emerging epidemic negatively impacting every country, age group, and economy (Papatheodorou et al., 2018). Malta has a remarkably high percentage of its population (10.1 %) diagnosed with T2DM when compared

to other European countries (2-5%) (World Health Organisation, 2016), and this could be due to strong familial predisposition and obesity (Formosa et al., 2012). Maltese diet also plays a major role in the high prevalence of T2DM within its population. Malta`s history of different colonisation has led to a drift from the traditional Mediterranean diet. The Maltese diet tends to include more red meat, fried food, fats, carbohydrates, and refined sugar, leading to obesity and T2DM (Rocchiccioli, O`Donoghue and Buttigieg, 2005).

Other risk factors associated with the development of this disease include a sedentary lifestyle (Zimmet, Alberti and Shaw, 2001), lack of physical activity (Hu et al., 2001), smoking (Manson et al., 2000), alcohol (Cullmann, Hilding and Ostenson, 2012), obesity and diabetes in close relatives (Chege, 2010). Early identification, prevention, and management of these risk factors are crucial to evade serious complications such as ulcerations and amputations (El Sadig and Al Maskari, 2007).

Many often neglect the signs and symptoms of T2DM because the consequences of this disease are not manifested immediately. However, the damage is often done before symptoms appear (Ramachandran, 2014). In 90-95% of T2DM patients, no symptoms are present during the early stages and often go unnoticed (Cilia, 2007). This leads to late diagnosis, increasing the risk of developing T2DM complications (Papatheodorou, 2017). Polyuria, polydipsia, weight loss and fatigue are common symptoms associated with T2DM (Warren, 2002). Other symptoms include genital itching, stomatitis, visual disturbances, fatigue, confusion, and balanitis (Drivsholm et al., 2005). Awareness of these signs and symptoms related to T2DM and regular monitoring of blood glucose levels, especially when these symptoms are present, would aid in early diagnosis and prevent complications.

WHO Diagnostic Criteria	
Diabetes	
Fasting Plasma Glucose	>7.0mmol/L
2-Hr Plasma Glucose	11.1mmol/L
Impaired Glucose Tolerance	
Fasting Plasma Glucose	<7.0mol/L
2-Hr Plasma Glucose	7.8 and <11.1mmol/L
Impaired Fasting Glucose	
Fasting Plasma Glucose	6.1-6.9mmol/L
2-Hr Plasma Glucose	<7.8mmol/L

Figure 2.2: WHO diagnostic criteria for Diabetes Mellitus. Retrieved from Setacci et al. (2009)

According to WHO, diabetes can be diagnosed by one of the following methods (Cox & Elelman, 2009).

1. A single raised fasting plasma glucose level (>7mmol/L) accompanied by symptoms such as polyuria, polydipsia, polyphagia, and weight loss.
2. Multiple raised values of fasting plasma glucose level (>7mmol/L).
3. Oral Glucose Tolerance Test (OGTT) giving a high plasma glucose level (>11.1mmol/L) after 2 hours of receiving the oral dose.

Additionally, an HbA1c ≥ 6.5% was recommended by the International Expert Committee in July 2009 as a diagnosis of diabetes mellitus. Treatment usually includes diet control, physical activity, oral hypoglycemic agents, or insulin.

Complications of Type 2 Diabetes Mellitus

Long-term uncontrolled blood glucose levels increase the risk of several short-term and long-term complications and may lead to premature death. One in four premature deaths in Malta is related to T2DM (Rocchiccioli, O`Donoghue and Buttigieg, 2005). Complications of T2DM can be divided into two major categories; microvascular and macrovascular complications (Deshpande et al., 2008). Microvascular complications are more common (Deshpande et al., 2008), including neuropathy, nephropathy, and retinopathy. Macrovascular complications may include cerebrovascular disease, cardiovascular disease, and PAD (Papatheodorou et al., 2018). Vascular disease and peripheral neuropathy are known to cause foot ulcerations (Pecoraro, Reiber, and Burgess, 1990); therefore, regular neurological and vascular examinations are essential to prevent diabetic foot complications (Wu et al., 2007). Other complications include resistance to infections, dental disease, and birth complications (Deshpande et al., 2008)

Reducing the risk of developing T2DM complications can be done by attaining normoglycaemia (HbA1c < 6%) (Stratton et al., 2000). In patients with T2DM, controlling the blood sugar level for at least 10 years would lead to increased health benefits such as lower rates of myocardial infarction and diabetes-related deaths (Holman et al., 2008).

Type 2 Diabetes Foot Complications

Diabetes is a big concern all around the globe due to its complications, most of which affect the foot (Aziz, 2013). Foot complications are frequently observed in patients with diabetes mellitus. These can present in various forms, ranging from minor issues to severe conditions that may threaten the limb or the patient's life. Proper management of these complications can involve medical treatments and even lengthy hospital stays (Hussain & Kalam, 2020).

An increase in T2DM worldwide has led to increased T2DM-related complications and costs (van Houtum, Lavery and Harkless, 1996). According to the World Health Organization, diabetic foot complications treatment in high-income countries uses up to 15-25% of healthcare resources for diabetes. It is estimated that 15-25% of patients with diabetes will develop a diabetic foot ulcer during their lifetime which is associated with a higher risk of amputations and premature mortality (Abbott et al., 2002 & Wild et al., 2004).

It is crucial to note that in Malta, most patients (roughly 80%) who undergo major lower extremity amputations suffer from diabetes. Furthermore, diabetic patients who undergo this procedure have a 5-year mortality rate of 60%, which is significantly higher than the 46.4% rate observed in non-diabetic individuals (Theuma et al., 2017). It is concerning that 85% of lower extremity amputations happen due to foot ulcerations that were not treated properly and in time (Pecoraro, Reiber and Burgess, 1990). Patients with diabetes mellitus typically experience gradual and frequent foot amputations (Spoden et al., 2019; McGuire et al, 2021).

Even though there has been a decrease in the number of amputations within the general population, this change is not observed within the diabetic population (Vamos et al., 2010). In fact, amputation rates in the diabetic population were 22.8 times higher than those of the general population (Holman, Young and Jeffcoate, 2012). Effectively managing diabetic feet and taking preventive measures are crucial in reducing the likelihood of severe outcomes.

Diabetic foot syndrome is characterised by foot ulcers associated with neuropathy, PAD, and infection (Tuttolomondo et al., 2015). In the upcoming sections, we will provide a comprehensive review and analysis of diabetic foot complications, including PAD, neuropathy, and neuroischemia.

Peripheral Arterial Disease

Peripheral arterial disease is a condition characterised by obstruction of the arteries of the lower limb in a process known as atherosclerosis (Hankey, Norman and Eikelboom, 2006). The most accepted definition of PAD is an ABPI of 0.9 or less, with this being 95% accurate in diagnosis according to some studies (Dormandy and Rutherford, 2000). This will be discussed in greater detail further on. Old age, CAD, systolic and diastolic hypertension, smoking and HbA1c >7% have been known to significantly increase the risk of developing PAD (Agarwal, 2012; Weragoda et al., 2016). Furthermore, the risk of developing of PAD increases with longer exposure to these risk factors (Weragoda et al., 2016). Since PAD is mostly asymptomatic, it could take several years until severe atherosclerosis occurs and symptoms starts to appear (Weissberg, 2000).

Agarwal et al. (2012) performed a study to assess the prevalence of PAD in T2DM patients. The study included 146 subjects and an ABPI <0.9 was used to determine the presence of PAD. PAD was found to be present in 14.4% of participants, with a slightly higher prevalence in women (14.9%) than in men (13.9%).

PAD is a frequent complication among individuals with T2DM. It affects 3%-10% of the general population and this percentage increases to 15%-20% for those aged over 70 (Formosa et al., 2013). It has been observed that among individuals aged 50 years and above with T2DM, the prevalence of PAD can increase up to 29% (Hirsch et al., 2001). Additionally, around 50% of patients diagnosed with diabetic foot ulcer have coexisting PAD and may experience chronic ischaemic pain (Brownrigg et al., 2015). The presence of PAD makes it more difficult for ulcers to heal therefor increases the risk of amputations, morbidity, and mortality (Brownrigg et al., 2015). Ulcer healing rates decreased from 84% in patients without PAD to 69% in patients with PAD while major amputation rates increased from 2% in patients without PAD to 8% in patients with PAD (Siersma et al., 2013). Apart from lower extremity complications, PAD has also been associated with an increased risk of cardiovascular and cerebrovascular disease (Brownrigg et al., 2015).

Hobaus et al. (2020) performed a study with the aim to examine how strict glycaemic control affects all-cause mortality in patients with PAD and T2DM. The study split 367 subjects with PAD into three groups based on their glycaemic control. The study showed that patients with

strict glycaemic control had an increased chance of survival (75%) when compared to those with lenient glycaemic control (58.9%).

Patients with diabetes often experience more extensive and severe peripheral vascular problems, especially in the thigh and leg regions (Brownrigg et al., 2015). It is quite common for the tunica media to become calcified, which can result in a decrease in tissue perfusion. In patients with diabetes, the development of new arteries as a result of large artery occlusion is often impaired compared to those without diabetes (Vivo et al., 2005). Patients with diabetes experience impaired mechanisms that would normally increase perfusion, minimise tissue damage and initiate the healing process when damage occurs from ischaemia (Brownrigg et al., 2015).

Physiology of PAD

Hyperglycaemia and insulin resistance are two major factors in development of atherosclerosis (Paneni et al., 2013). Metabolic abnormalities cause an increase of reactive oxygen species which causes endothelial dysfunction and inflammation which ultimately leads to atherothrombosis (Paneni et al., 2013). Diabetic and non-diabetic patients with PAD have remarkably similar pathophysiology of PAD (Marso and Hiatt, 2006). The difference is that in diabetic PAD there is increased production of advanced glycation end products, increased oxidative stress, increase in inflammatory markers and dyslipidaemia which may worsen the disease (Beckman, Creager, Libby, 2002).

The high plasma glucose level in patients with diabetes leads to excess formation of advanced glycation end products which are involved in vascular damage (De Vos et al., 2013). Increase in oxidative stress brings about damage to vascular structures such as endothelial dysfunction due to inactivation of Nitrous Oxide (Victor et al., 2009).

High level of Low-Density Lipoprotein cholesterol is often present in patients with diabetes, which is generally oxidised to form oxidised Low-Density Lipoprotein (ox-LDL), which is a very significant factor in the development of atherosclerosis. A determining factor in the progression of PAD is inflammation, which is a known risk factor for atherothrombosis

(Beckman, Creager, Libby, 2002). There is also a strong association between C-Reactive Protein (CRP) and the development of PAD (Ridker et al., 1998). Additionally, it has been discovered that CRP levels are abnormally high in individuals with diabetes. Research has demonstrated that diabetes-related impairments in endothelial function can increase the likelihood of developing PAD (Veves et al., 1998).

Signs and Symptoms of PAD

In the clinical setting, PAD may present as asymptomatic, symptomatic, or critical limb ischaemia (Hirsch et al., 2006). The incidence of asymptomatic PAD tends to be much higher than symptomatic PAD (Hooi et al., 2001). Many patients also present with atypical leg pain which is not usually associated with PAD (Zemaitis, Boll & Dreyer, 2023). Signs of PAD on examination may include inability to feel peripheral pulses, pain, loss of skin colour, loss of muscle mass, hair loss, and cold extremities (Zemaitis, Boll & Dreyer, 2023). Symptoms usually appear extremely late with intermittent claudication or critical limb ischaemia (CLI) (Feringa et al., 2007). CLI is the most severe form of PAD typically consisting of pain in the feet or toes even at rest. In some patients, the first sign of CLI would be ulcer formation and necrosis (Schorr & Treat-Jacobson, 2013).

Intermittent claudication is by far the most frequent symptom of PAD (American Diabetes Association, 2003). It involves pain in the calf muscle during exercise, alleviating by rest (American Diabetes Association, 2003). Although most of the time the pain in IC is characterised by cramping pain, weakness, leg fatigue, pressure, or aching (Zemaitis, Boll & Dreyer, 2021). During exercise, the blood supply demand by the leg muscles increases, however due to the inadequate blood flow, the body is unable to meet the demands of the increased metabolic activity resulting anaerobic respiration and lactic acid formation (Norgren et al., 2007; Olin & Sealove, 2010). The pain/discomfort of PAD is often felt a level distal to that of the blockage (Olin and Sealove, 2010). Therefore, patients with occlusion within the aortoiliac artery would have symptoms in the thigh and buttock muscles while patients with femoropopliteal occlusion would have symptoms in their calf muscles (Zemaitis, Boll & Dreyer, 2021). The walking distance before the pain starts is not always indicative of disease

severity as other factors may come into play such as incline, walking pace and terrain (Zemaitis, Boll & Dreyer, 2021).

Intermittent claudication tends to progress to disabling claudication or critical limb ischaemia in 20 to 30% of patients over a period of 10 years (Hirsch et al., 2006). Furthermore, around 5% of patients with intermittent claudication require amputation within a 5-year period (Hooi et al., 2004; Twine et al., 2009). Ischaemic rest pain is another symptom of PAD. It occurs with more severe disease when blood supply is inadequate even at rest. These patients often complain of pain in their feet or toes, which worsens at night. Dangling the leg by the side of the bed may reduce the pain and discomfort since gravity would help in increasing the blood flow towards the foot (Zemaitis, Boll & Dreyer, 2021).

According to Bendermacher et al. (2007) most PAD patients are either asymptomatic or have atypical leg symptoms. This was confirmed in a study by Ramos et al. (2009) which included 6,262 participants aged 35-79. 4.5% of the cohort had been diagnosed with PAD (ABPI<0.9). Only 0.62% of the participants with PAD reported symptoms of IC, which increased to 14% in participants aged 75-79. A study by Adler et al. (2014) which included 229 participants with PAD, it was also shown that most participants (56%) were asymptomatic. Furthermore, 24% had atypical leg pain, and only 20% had symptoms of claudication.

The most severe presentation of PAD is critical limb ischaemia (CLI) (Swaminathan et al., 2014) characterised by ischaemic rest pain, and gangrene or ulceration in the lower extremity (Henry et al., 2014). CLI is often present in elderly patients with several co-morbidities such as diabetes, renal problems, cardiac problems amongst others (Tsetis and Belli, 2004). Prognosis of patients with CLI is extremely poor with only 25% see their condition resolved. Moreover, 30% will undergo amputation, and 25% will die (Norgren et al., 2007).

Since most cases of PAD are asymptomatic (Hooi et al., 2001; Hirsch, 2001) and therefore most cases are not detected in the primary health care setting (Lee et al., 2011). The absence of PAD symptoms could be attributed to several reasons. Patients with PAD tend to limit their physical activity or do not sustain a walking pace that increases the blood demand to the lower extremities (McDermot, Guralnik & Ferrucci, 2008). In a study by McDermot et al. (2001) it was shown that when walking for six minutes, 89% of patients with asymptomatic PAD who were also inactive had developed leg pain. Another reason could be that since most of PAD

patients are elderly, they attribute the symptoms to the natural consequences of aging (Zemaitis, Boll & Dreyer, 2021).

Peripheral neuropathy also plays a part in masking PAD symptoms especially in patients with T2DM. pain perception is blocked in peripheral neuropathy and therefore symptoms of claudication will not be present (American Diabetes Association, 2003). The high prevalence of PAD and peripheral neuropathy in T2DM patients increases the risk of gangrene and ischaemic ulcerations (Ogbera et al., 2015; American Diabetes Association, 2003). Progression of asymptomatic PAD over a 1-year period was investigated by Mohler et al. (2012). Duplex Ultrasound, ABPI and leg pain assessment were used to measure the state of PAD. The study showed that there was an increased in the chances of patients developing symptoms of IC and a significant decrease in 6-minute walking distance. Furthermore, 35% of subjects had developed new or progressive lesions.

Even though PAD may be asymptomatic, this does not mean that there is a decreased risk of mortality than in patients with symptomatic PAD. In fact, in a study by Daoud et al. (2011) it was shown that both patients with and without symptoms of PAD had extremely high mortality rate.

Diagnosis of PAD

Early examination and detection of PAD lead to a decrease in the risk of ulceration and amputation (Brownrigg et al., 2015). There are still concerns about understanding and interpreting various diagnostic tests for individuals with T2DM. One crucial aspect is diagnosing PAD in those with T2DM, even if their feet appear to be intact. This is necessary to identify those who are at risk of developing complications and to prevent such complications from occurring through early management of the disease (Prompers et al., 2007).

It can be difficult to diagnose PAD in patients with T2DM due to the prevalence of distal sensory neuropathy. This condition is often present in individuals with diabetes and may obscure symptoms of intermittent claudication and rest pain (Brownrigg et al., 2015). Ulceration, oedema and infection in patients with T2DM are often present and these may hinder

the performance of diagnostic tests (Brownrigg et al., 2015). T2DM patients are less likely to experience symptoms of intermittent claudication and show poorer lower extremity functioning which could be because of peripheral neuropathy (Dolan et al., 2002).

While examining peripheral pulses may not be enough to identify PAD, the absence of these pulses may serve as a good predictor for cardiovascular disease (Brownrigg et al., 2015). It is crucial to palpate both the dorsalis pedis and posterior tibial artery, as about 30% of individuals are born with a deficiency in the dorsalis pedis artery (Mohler, 2003). Additionally, environmental temperature is known to significantly affect the palpation of foot pulses (Brownrigg et al., 2015). However, the presence or absence of peripheral pulses does not give any information regarding the decrease in tissue perfusion (Lundin et al., 1999).

Doppler Waveform

A handheld doppler can be used to assess macro perfusion from the posterior tibial and dorsalis pedis arteries. This is the most common tool used to assess peripheral circulation and be used as a stand-alone test or part of the ABPI procedure (Chen et al., 2012). This is a good bedside test to exclude PAD in patients with or without diabetes (Alavi et al., 2015).

The procedure involves the application of gel over the artery to act as a medium for sound waves to travel through. The sound waves from the blood traveling through the artery are then detected by the doppler probe (Suzuki and Kawarada, 2012).

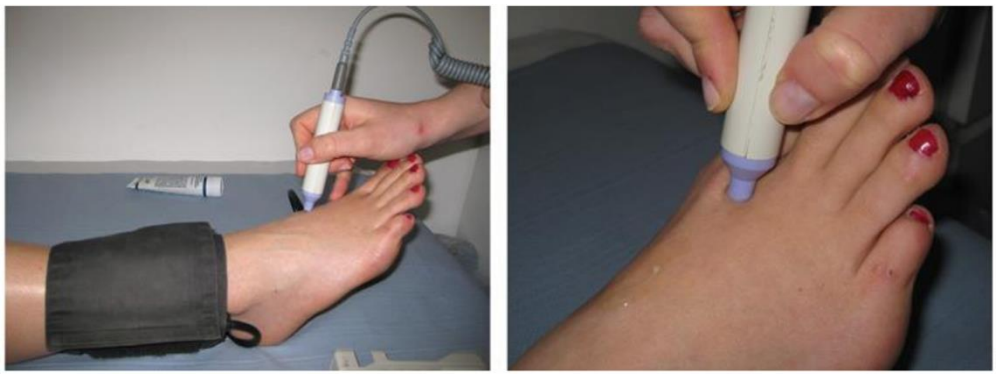

Figure 2.3: Doppler application. Retrieved from Bailey, Griffin and Scott (2014).

The doppler probe should be held around an angle of 60º against the flow of blood as seen in the figure above. The doppler probe is then moved around to find the best signal from the pulsating artery (Bailey, Griffin and Scott, 2014). Signals are classified as triphasic, biphasic, monophasic, or absent. Triphasic and biphasic pulses are considered to be normal while monophasic pulses are considered to be pathological (Eagle, 2006; Poe, 2012). A triphasic waveform consists of forward blood flow during cardiac systole, backward flow during early diastole, and forward flow during late diastole (Brownrigg et al., 2015). Loss of the final wave in biphasic pulses occurs due to loss of forward flow during late diastole related to problems with arterial wall (Poe, 2012).

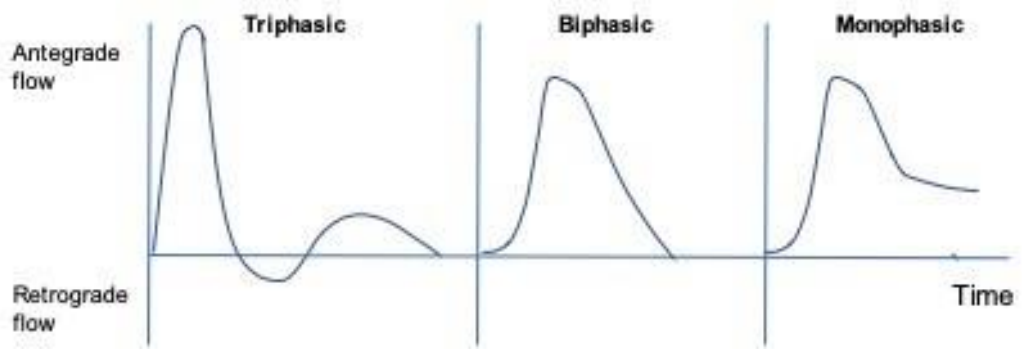

Figure 2.4: monophasic, biphasic & triphasic waveforms Retrieved from Robinson & Song (2021)

A Tehan and Chuter (2015) study found that the interpretation of visual Doppler waveform is more reliable than audio interpretation. The study also found poor reliability in a small cohort of practitioners. The study recommended that rather than using the Doppler waveform on its own, more than one method to assess lower limb circulation. Excellent interrater reliability of the spectral Doppler waveform interpretation was reported by Formosa et al. (2018). The use of both Doppler waveform and ABPI when screening for PAD in patients with diabetes is recommended by Formosa et al.,2013.

Ankle Brachial Pressure Index

ABPI is one of the methods used to diagnose PAD; however, over the years, its reliability within the literature has been challenged, especially in cases where arterial calcification is

present (Formosa et al., 2013). Reverse flow is lost in monophasic and biphasic pulses, while in severe PAD pulses may even be absent.

ABPI compares the systolic pressure at the brachial artery in the arm with the systolic pressure at the ankle. A manual blood pressure cuff is placed just above the ankle while using a hand-held doppler probe to locate the dorsalis pedis or posterior tibial artery (Zemaitis, Boll & Dreyer, 2021). The blood pressure cuff is inflated until the doppler sound is cut off. The systolic blood pressure at the ankle is recorded when the blood pressure cuff starts to deflate and the sound on the doppler is heard again. The systolic pressure of the brachial artery is measured by placing the blood pressure cuff on the upper arm and the hand-held doppler probe on the ulnar or radial artery at the wrist. The systolic blood pressure of each ankle is then divided by the systolic blood pressure of the arm.

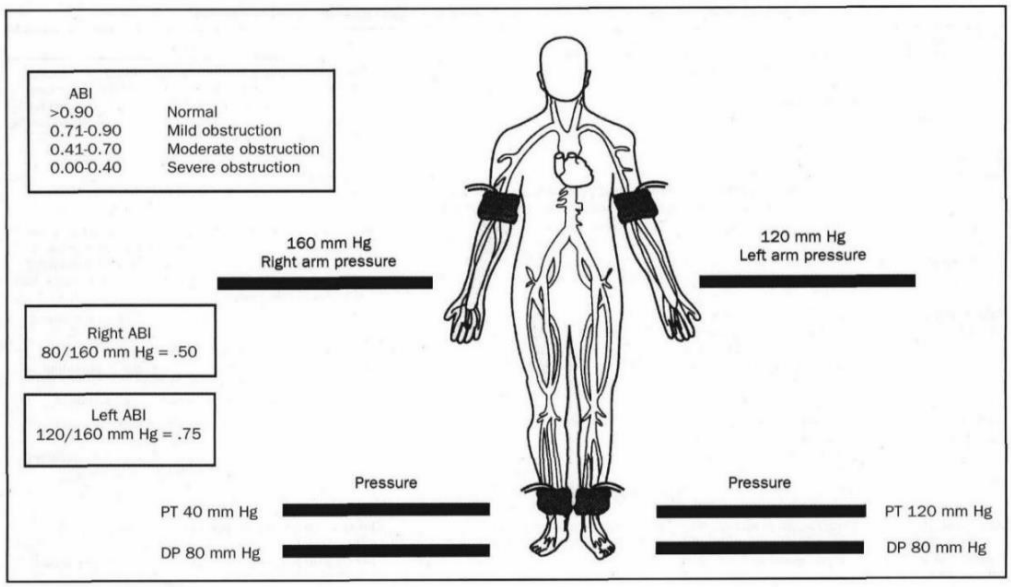

Figure 2.5: ABPI. Retrieved from Olin and Sealove (2010).

In patients with diabetes or renal problems, calcification of the arterial wall may occur which may give a falsely elevated reading (ABPI>1.3) (Santoro et al., 2018). In 5-10% of patients with diabetes, ABPI is non-diagnostic due to calcification of arteries (Raines et al., 1976). Calcification of the arteries does not lead to a decrease in the diameter of the lumen and therefore blood flow is not obstructed (Brownrigg et al., 2015).

According to Zemaitis et al. (2021), the highest systolic blood pressure of both arms should be used when compared to the ankle systolic pressure due to upper extremity blood pressure discrepancy which would give inaccurate ABPI value. The accuracy of ABPI can be enhanced if the patient lies supine a minimum of five minutes before systolic blood pressure measurements are taken so that enough time is given for the blood pressure to stabilize (Zemaitis et al., 2021).

100% specificity has been observed for values between 1 and 1.3 in identifying healthy individuals (Norgern et al., 2007). The average ABPI value was found to be 1.14 (range from 1.05-1.25) in a study by Male, Coull and Black (2007), which included 24 healthy participants aged 20 to 40. According to Al-Qaisi et al. (2009) although many studies prove that normal ABPI values are higher than 1, the reason the American Diabetes Association stand with the decision that the normal minimum ABPI value is 0.91 and higher is because the respiratory phase is not controlled during ABPI, and this may influence the blood pressure reading of upper and lower extremities. The sensitivity and specificity of a 0.9 ABPI cut-off point are around 95% accurate for diagnosing angiographically PAD in patients with symptomatic PAD (Norgen, 2007; Doobay and Anand, 2005).

Toe Brachial Pressure Index

TBPI is less affected by calcified arteries than ABPI. It involves a similar procedure to ABPI but is more difficult and involves more time (Brooks et al., 2001). The TPBI procedure involves the measurement of systolic pressure at the brachial artery and systolic pressure at the toe (Tehan et al., 2006). The systolic pressure of the toe is then divided by that of the toe similar. TBPI is used when calcification of the arteries is present or when there are elevated levels of ABPI (Norgren et al., 2007). Although calcification of arteries is common in patients with diabetes, arteries of the toes are less likely to be affected, making TBPI a more useful tool in identifying PAD (Høyer, Sandermann & Peterson 2013). A cut-off point for diagnosis of PAD using TBPI still remains unclear and several studies have recommended TBPI < 0.7 (Høyer, Sandermann & Peterson 2013). A TBPI of <0.7 is highly suggestive of PAD (Petrova & Shanahan, 2014). TBPI <0.75 has a sensitivity of 61% in identifying PAD in patients with diabetes and neuropathy, and 65% in patients with diabetes without neuropathy (Williams,

Harding & Price, 2005). According to Quong et al. (2016) TBPI values within healthy subjects should be between 0.94 and 0.98.

Huge discrepancies and inconsistencies between different screening modalities when diagnosing PAD were identified in a study by Midolo Azzopardi et al. (2018). The study included 100 limbs from 50 participants with T2DM. Pulse palpation, waveform analysis, ABPI, absolute toe pressure (ATP), TBPI, and transcutaneous oxygen pressure (TCPO) were compared. When using the Doppler waveform, 93% of participants were found to have PAD. Results for TBPI, ABPI, ATP, TCPO and pulse palpation were found to be 72.0%, 57.0%, 35.0%, 30.0%, and 23.0% respectively. This highlights the fact that medically validated tests commonly used in the clinical setting produce different results when it comes to diagnosing PAD. In cases where the presence or absence of PAD cannot be determined with certainty, additional tests such as thermography may be considered as a useful complementary tool. The application of thermography in PAD will be discussed in detail further on in this chapter.

Peripheral Neuropathy

Aetiology & Epidemiology

Diabetic neuropathy is an insidious, variated pathology that effects numerous body systems. Microvascular damage occurring due to long term uncontrolled blood glucose level can lead to diabetic neuropathy with the most common type being diabetic peripheral neuropathy (Veresiu et al., 2015). Symptoms may include numbness, paraesthesia, and hyperesthesia. However, in around 50% of patients, diabetic peripheral neuropathy may be asymptomatic (Deli et al., 2013). This is often associated with increased risk of foot ulcers and diminished sensation in the foot (Lee et al., 2015). DPN often has a subtle onset, however, it could become chronic if not treated promptly and effectively.

The primary risk factor for peripheral neuropathy is hyperglycaemia (Deli et al., 2013; Deshpande et al., 2008). Approximately 8% of individuals recently diagnosed with diabetes are also diagnosed with neuropathy. However, this percentage significantly increases to 50% in patients who have been living with diabetes for an extended period of time. Additionally,

25% to 62% of patients with idiopathic peripheral neuropathy are reported to have pre-diabetes (Deli et al., 2013; Papanas, Vinik & Zeigler, 2011). Other risk factors include age, cigarette smoking, hypertension, and alcohol consumption (Deli et al., 2013).

Studies have shown that achieving glycaemic control in patients with T2DM decreases the progression of diabetic peripheral neuropathy (Tang et al., 2019). However, glycaemic control does not seem to influence diabetic peripheral neuropathy in patients with T2DM (Tang et al., 2019).

Physiology

The mechanisms of pain sensations in neuropathy are poorly understood. Pain intensity in patients with DPN is not associated with the severity of neuropathy and can also occur even when no nerve damage is present (Sorensen et al., 2006). Diabetes leads to nerve dysfunction and death through increased extracellular protein glycation, increased intracellular glucose in nerve and vascular tissue, and microvascular injury (Deli et al., 2014).

Oxidative stress is thought to be the main mechanism leading to nerve damage in diabetes. This oxidative stress is caused by microangiopathy within the nerve (Deli et al., 2014). Hyperglycaemia leads to oxygen-free radical generation that in turn causes endothelial dysfunction and ischaemic nerve damage (Tang el al., 2019). Other mechanisms leading to nerve damage include deposits Advanced Glycation products in the nerve, elevated levels of saturated fatty acids, increase synthesis of diacylglycerol, and altered ion channels functions (Deli et al., 2014).

Damage to the peripheral nerves results in hyperexcitability in the primary afferent nociceptors and the generation of spontaneous impulses within the peripheral nerve's axon and dorsal root ganglion (Veves et al., 2008). Pain sensation without an external stimulus is due to abnormal creation of these impulses within the nociceptive pathways (Baron, Binder & Wasner, 2010). Altered ion channels functions can enhance excitability due to persistent sodium currents. Activation of Polyol pathway in diabetic neuropathy leads to reduced activity of the sodium-potassium pump and sodium accumulation inside the axon (Kuwabara & Misara, 2008).

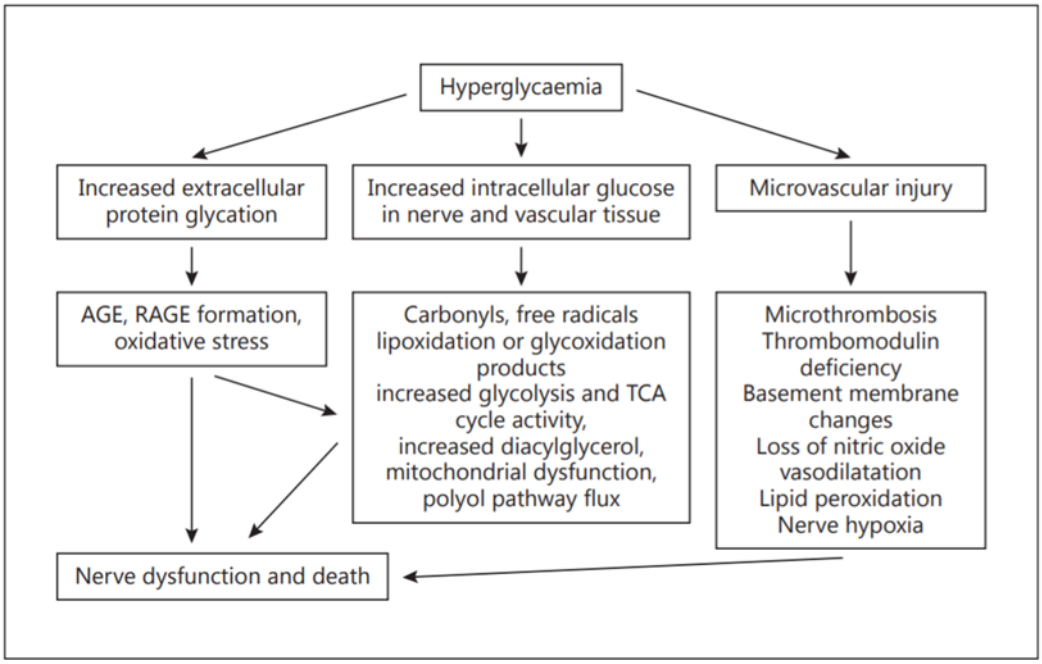

Figure 2.6: The pathogenesis of diabetic neuropathy

Signs and Symptoms

In diabetic peripheral neuropathy, nerve endings in the hands and feet are affected. Numbness, pricking, and burning sensations are some of the common symptoms in patients with diabetic neuropathy (Amelia, Wahyuni & Yunanda, 2019). Diabetic peripheral neuropathy can cause issues with balance, loss of sensation in feet, and a major contributor to non-traumatic lower limb amputations (Vinik et al., 2013; Lamparter et al., 2014). It is often difficult to be diagnosed due to asymptomatic onset and abnormal presentation (Veresiu et al., 2015).

In a study by Pop-Busui et al. (2017) that included 4097 subjects, T2DM was found to be present in 90.6% of patients. Among T2DM subjects, 19.4% were found to diabetic neuropathy. Neuropathy should be taken seriously as it could lead to disruption of function such as muscle weakness and loss of reflexes at the ankle (Amelia et al., 2019). These can cause changes in gait as well as changes in the shape of the legs and foot such as hammer toes (Amelia et al., 2019).

Diagnosis

Earlier identification of peripheral neuropathy in T2DM allows for prevention of foot ulcers and amputations through better management, timely intervention, and lifestyle change (Phillips et al., 2014). Diabetic peripheral neuropathy often develops silently over time making it difficult to be detected early (Phillips et al., 2014). Several methods can be used to detect DPN such as physical examination scoring systems, nerve conduction studies, quantitative sensory testing, and electrodiagnostic test (Forouzandeh et al., 2005). 128 Hz tuning fork and 10g monofilament are amongst other tools to have been successful in screening and assessing peripheral neuropathy in patients with T2DM (Brown et al., 2017).

The American Diabetes Association`s 2011 guideline recommended yearly screening for neuropathy in patients with diabetes using tools such as 10g monofilament, 128MHz tuning fork, pin prick sensation testing, and assessment of ankle reflexes (American Diabetes Association, 2011). Studies have shown that the 10g monofilament ant the 128MHz tuning fork have very good sensitivity and specificity when screening for diabetic neuropathy (Feng et al., 2009; Meijer et al., 2005).

10g Monofilament

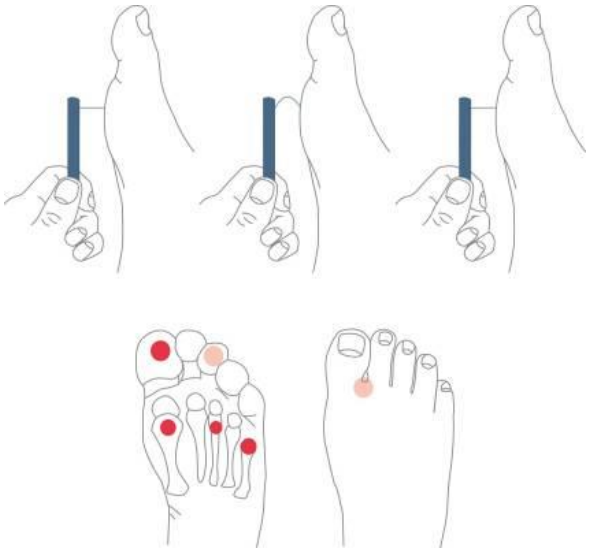

Figure 2.7:Monofilament testing. retrieved from Boulton et al. (2008)

Monofilament testing are commonly used in the clinical setting to screen for signs of peripheral neuropathy due to their availability and convenience (Slater et al., 2014). The 10g monofilament consists of an accurate handheld calibrated nylon thread that buckles when a 10g force is applied. When applied to the person`s skin, the monofilament provides a measure of pressure sensation ability. Before being applied to the foot, a demonstration of the sensation of the 10g monofilament should be applied on the upper arm (Boulton et al., 2008). The monofilament is applied on several specific points on the foot and the patient being examined is instructed to indicate every time the pressure is felt. Patients are instructed to close their eyes while being tested for more accurate results (Boulton et al., 2008). It is recommended that the 1st, 3rd, and 5th metatarsal heads and plantar surface of distal hallux are tested on each foot (Boulton et al., 2008).

The 10g monofilament is effective when screening for advanced neuropathy and identifying patients who are at a high risk of amputation and ulceration (Tan et al., 2010). In a systematic review by Feng et al. (2009) it was observed that the monofilament is an optimal tool in testing for diabetic neuropathy with sensitivity of 90% or higher. Hence, the monofilament can be an inexpensive, accurate and painless method of identifying diabetic neuropathy.

128 Hz Tuning Fork

The 128MHz tuning fork is also used when screening for peripheral neuropathy. The test involves comparing how long the patient feels the vibration sensation compared to the examiner. The tuning fork is activated by being hit against the palm of the hand. The tuning fork is then applied to a bony prominence where neuropathy is unlikely such as the elbow or wrist, for familiarisation with the vibration sensation. The ankle and the distal area of the big toe are the typical locations for vibration testing. (Azzopardi et al., 2017).

The patient is instructed to indicate when the vibration sensation stops. When the person being tested says the vibrations have stopped, the examiner places a tuning fork on their wrist. If the examiner can still feel the vibrations, it suggests that the person being tested has a reduced ability to sense vibrations (Boulton et al., 2008).

Several clinical guidelines recommend the use to 10g monofilament and vibration perception testing as screening tools to identify diabetic peripheral neuropathy and predict foot ulcerations (American Diabetes Association, 2018). It is commonly used in the clinical setting to assess peripheral neuropathy due to its availability and convenience (Slater et al., 2014).

In a study by Wang et al. (2017) it was shown that monofilament testing as limited sensitivity and acceptable specificity when used a screening tool to identify diabetic peripheral neuropathy and therefor it needs to be used with other screening tools to diagnose DPN. Brown et al. (2017) recommended the use of 1g monofilament in addition with Norfolk Quality of Life Diabetic Neuropathy questionnaire (QOL-DN) for effective early detection of peripheral neuropathy. Furthermore, the authors concluded that the 128 MHz tuning fork and the 10g monofilament shouldn`t be used as primary tools to detect peripheral neuropathy but in addition to the QOL-DN and 10g monofilament.

Figure 2.8: 128Hz Tuning Fork

Patient history, physical examination, and tools such as the 128 MHz tuning fork and 10g monofilament are extremely important in diagnosing diabetic peripheral neuropathy, however several studies have questioned the reliability of these tools. Azzopardi et al. (2017) recommended the usage of different modalities when instruments when screening for vibration perception threshold and if results do not agree, further testing would be required. Therefore, a new, more effective tool is needed to aid in early diagnosis of diabetic peripheral neuropathy and other diabetic complications.

Screening for T2DM Foot Complications

Diabetes screening aims to detect individuals who show no symptoms but are at a high risk of developing the disease or its complications through suitable screening tests. By implementing appropriate, meticulous, and dependable screening and management protocols, one can potentially delay or even prevent severe complications related to diabetic foot.

It is crucial for patients with diabetes mellitus to undergo a comprehensive yearly foot evaluation to detect any potential risk factors for ulcers and amputations, as recommended by the American Diabetes Association (2018). The patient's medical records pertaining to diabetic complications such as ulceration, amputation, Charcot foot, vascular surgery, cigarette smoking, retinopathy, and renal disease must be recorded to achieve this. In addition, the examination should comprise examining the skin, evaluating foot deformities, and conducting a neurological and vascular assessment.

The American Diabetes Association (2018) recommends that neurological assessment involve using a 10-g monofilament test and at least one other assessment, such as pinprick, temperature, and vibration. The International Diabetes Federation (2015) recommends using a 10g monofilament or 128Hz tuning fork to assess neuropathy. Biothesiometer can be used for quantitative assessment of neuropathy.

For vascular assessment, the American Diabetes Association (2018), the International Diabetes Federation and the NICE guidelines (2014) recommend checking pulses in the legs and feet. the American Diabetes Association (2018) states that patients with claudication symptoms or decreased or absent pedal pulses should be referred for an ABPI and further vascular assessment if needed. The International Diabetes Federation recommends palpation of posterior tibial and dorsalis pedis arteries. ABPI (<0.9) may be used to quantify the disease. The NICE Guidelines (2014) recommend that patients who may benefit from revascularisation should be referred immediately.

The NICE guidelines (2014) recommend that patients with absent pulses, signs of peripheral neuropathy or other risk factors should have their feet inspected every 3-6 months. Furthermore, foot inspection should be every 1-3 months for high-risk patients with neuropathy or absent pulses with deformity, skin changes or previous ulcers.

Diabetes is highly prevalent in Malta, affecting 10.1% of the population. As a result, healthcare professionals are under immense pressure to provide timely and reliable foot screening services for diabetic patients. Consequently, there is a growing demand for dependable, efficient, secure, and timely screening techniques.

The increase in cutaneous temperature before an ulcer develops has already been reported in the literature (Lavery et al., 2007; Armstrong et al., 2007). Changes in foot cutaneous temperatures have also been reported to appear chronically in patients with T2DM foot complications suggesting that the use of thermography could be used as a screening tool to identify chronic diabetic foot complications (Gatt et al., 2018, Carabott et al., 2018, Bagavathiappan et al., 2010; Ilo, Romsi & Mäkelä, 2019) However, the use of thermography as a screening tool has yet to be tested. The purpose of this study is to determine if thermography can effectively screen for chronic diabetic foot complications. This is the first study of its kind.

Infrared Thermography

Infrared was discovered by accident by the scientist William Herschel in 1800 when trying to determine the temperature of the colours in the visible light spectrum. Different thermometers were placed on the different colours on the visible light spectrum and another thermometer was placed next to the red light to be used as control. Herschel noticed that the temperature increased steadily from blue to red. Furthermore, the control temperature was even warmer, which led to the discovery of infrared radiation.

Any object with a temperature above absolute zero (−273.15 °C) emits electromagnetic radiation. Furthermore, electromagnetic energy emitted by the environment can also absorbed by the object (Quesada et al., 2017). Physical laws relate the wavelength and intensity of this electromagnetic radiation to the surface temperature of an object (Holman, 1986). This allows temperature measurement of an object without physical contact.

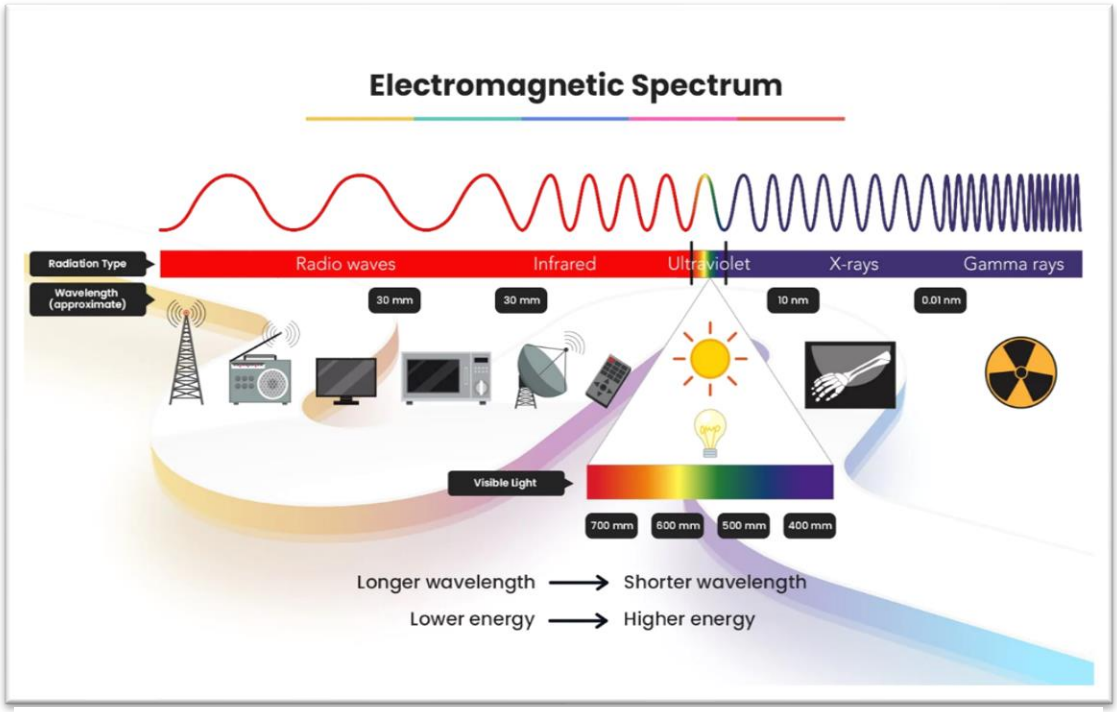

Figure 2.9: Electromagnetic Spectrum

Electromagnetic radiation between 400 to 700nm wavelengths is known as the visible spectrum which are visible to the human eye. Most objects on earth emit is much small amount of radiation and long peak wavelengths of radiation. An object at room temperature emits radiation with a peak intensity at a wavelength of 10 urn, which is referred to as infrared radiation. The radiation is invisible to humans as it is below the threshold that can be detected by our eyes. The objects seen by humans are due to photons reflecting in the same waveband as that emitted from a light source. Radiation in the infrared region of the spectrum is not visible by the naked eye, however, this can be felt as heat (Speakman, 1998).

By measuring the intensity of radiation emitted from the surface of objects at any wavelength, the surface temperature of an object could be determined. The wavelengths of objects with a temperature range of -10^{o}C to 50^{o}C with a peak spectral emission between 9-11 urn are in the infrared range of the electromagnetic spectrum. Therefore, this radiation can be measured by infrared thermography (Speakman, 1998). The principle behind infrared thermography is that the intensity of the infrared radiation emitted by an object is directly related to its temperature. The hotter an object is, the more infrared radiation it emits. Therefore, by detecting and measuring the amount of infrared radiation emitted by an object, it is possible to calculate its temperature.

There are several factors which could influence the measurement of surface temperatures of objects from the intensity of infrared radiation being emitted. One of the most important factors is the nature of the surface of the object that could affect the intensity of the emitted radiation.

A black body is an object that is a perfect emitter at all wavelengths. When an object emits less radiation at the same temperature than a black body, it is described as an imperfect emitter. The extent of imperfection of an emitter, can be known by a value that expresses the ability to emit radiation at the same wavelength when compared to a black body. This is known as emissivity value. The emissivity of a material is represented by a value between 0 and 1, with 1 representing a perfect emitter and 0 representing a perfect reflector. Therefore, objects with an emissivity value closer to 1 are perfect for thermographic imaging because the radiation emitted from the object would reflect its true surface temperature (Gatt et al., 2015).

Stefan-Boltzmann law describes the energy radiated from a black body, or grey body, in relation to its temperature (Yang et al., 2021). Most objects are considered a grey body which means that these objects are not fully efficient in absorbing radiation (Ozerov & Vorobyev, 2007). The Stefan-Boltzmann law can be divided into two parts. The first part describes the power radiated from a black body (Stefan, J. (1879).

$$\mathbf{P = \sigma A T^4}$$

P refers to the power radiated from a black body, σ refers to the Stefan Boltzmann`s constant, *A* refers to the body`s surface area, and *T* refers to the temperature.

The second part of the Stefan-Boltzmann law describes the power radiated from a grey body (Stefan, 1879).

$$\mathbf{j = e \sigma T4}$$

j refers to the power radiated from a black body, σ refers to the Stefan Boltzmann`s constant, *e* refers to power of a body to emit the energy radiated into it, and *T* refers to the temperature.

When using an infrared camera to measure the temperature of an object, the emissivity of the material being measured must be known since this influences the accuracy of the temperature measurement. The emissivity value varies between 0 to 1, with 0 being the perfect reflector and 1 being the perfect emitter (Wisniak, 2002). The emissivity value of a material depends on

its composition, surface finish, and other factors. For example, a shiny, reflective surface will have a lower emissivity value than a rough, matte surface, as the shiny surface reflects more of the infrared radiation and emits less. Biological materials have been found to have an emissivity of infrared radiation between 0.9 to 0.97 (Speakman, 1998). This high emissivity is thought to be due to high water content in biological materials.

Infrared Thermal Camera

Infrared thermal cameras work by detecting the infrared radiation emitted by objects and converting it into an image that is visible to the human eye. The image produced by thermal cameras is known as a thermogram. This technique is built on the premise that all objects emit infrared radiation. These cameras can detect and measure the temperature of objects without the need for physical contact, making them useful in a variety of applications.

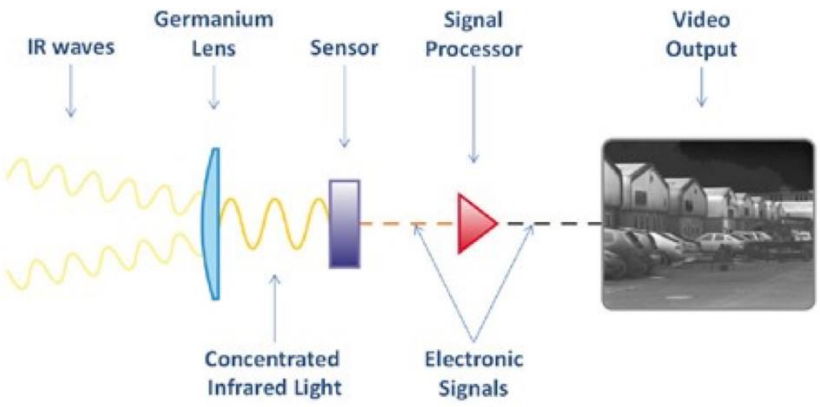

Figure: 2.10: How IR Thermal Camera Works

A specialized type of sensor called a microbolometer is used in thermal cameras to detect infrared radiation. The microbolometer is made up of an array of tiny pixels, each of which is sensitive to the infrared radiation emitted by objects. These pixels heat up when hit by infrared radiation and change in temperature is detected and converted into an electrical signal (Rai, 2018).

The electrical signal from each pixel is then processed and a thermogram is created. Different colours are assigned to each pixel based on its temperature, creating a color-coded image showing the examined object's temperature distribution (Rai, 2018).

Thermography in the Medical Setting

Human beings are known as homeotherms, meaning we could sustain body temperatures through heat loss and heat production mechanisms, regardless of the ambient temperature (Biederman-Thorson, Schmidt & Thews, 2013). The body`s core temperature is usually kept at 37^{o}C. Thermoregulatory mechanisms involve mostly behavioural adjustments to the surrounding temperature and autonomic nervous response (Adam et al., 2017). Responses from the autonomic nervous system to achieve thermal stability include cutaneous vasomotor and sweating response (Biederman-Thorson et al., 2013), therefor any temperature changes could be indicative of disease.

The human body often emits more heat radiation than it absorbs since the environment is cooler. However, when the body is close to warmer objects or environments, more radiation is absorbed resulting in an increase in temperature (Priego Quesada et al., 2017). According to Wein`s Law, the energy emitted from the human body is in the infrared region of the electromagnetic spectrum.

The skin has an emissivity value of 0.98, making it ideal for thermographic imaging (Lahiri et al., 2012). Highly reflective objects are not ideal for thermographic imaging as most outgoing radiation is reflected from the environment (Priego Quesada et al., 2017).

The infrared thermography is a non-contact, non-invasive and fast approach of measuring temperature while being safe for both the patient and the physician (Huang et al., 2011). It also offers real time visualization of the body`s cutaneous temperature without affecting the cutaneous temperature (Tan et al., 2009). Improvements in technology have led to improved image quality and speed of image capture with thermal cameras nowadays being used in different settings including in medicine for diagnosis of different pathologies.

Lawson first used infrared thermography in the medical setting in 1956 when he discovered the relationship between high cutaneous temperature and breast carcinoma (Lawson, 1956). Since then, thermography has been widely used in the medical setting such as urology, dentistry, oncology, dermatology (Lahiri et al., 2012), inflammatory osteoarthritis, Rheumatism, Complex Regional Pain Syndrome, fever screening (Ring and Ammer, 2012) and pain evaluation (Jones, 1998). Overtime more research is being done in identifying changes in cutaneous temperature suggesting that thermography could be used as a predictor of foot ulcerations in patients with diabetes (Staffa et al., 2016) with some research stating that an increase in temperature could be present a week before an ulceration appears (Armstrong et al., 2007; Sun et al., 2006). Infrared thermography has been widely used to efficiently and effectively screen persons to detect elevated body temperature during the midst of the covid pandemic (Fiscal et al., 2022).

The Use of Thermography in Identifying Diabetic Foot Complications

Early identification and treatment of diabetic foot disease can prevent unwanted complications such as ulcerations or amputations in the lower limb. Lower limb amputations are commonly preceded by diabetic foot ulcer, representing one of the highest numbers of hospital admissions leading to serious economic issue around the world (Noor, Zumbair & Ahmad, 2015)

Several studies have shown that changes to plantar cutaneous temperatures of the foot could be indicative of diabetic foot complications (Armstrong et al., 2007; Lavery et al., 2004). However, changes in temperature can be too small to be detected manually (Murff et al., 1998). Symmetrical pattern of the cutaneous temperatures of both feet is present in healthy individuals, while asymmetry between limbs is often indicative of disease (Gatt et al., 2015). The cutaneous temperature of an area supplied by a stenotic artery may have a decreased temperature. The difference in temperature will depend on the severity of occluded areas, function of the endothelium, development of collateral circulation and autonomic activity (Huang et al., 2011). Ischaemia, neuropathy, infection, or a combination of these factors could all lead to change in cutaneous temperature of the diabetic foot (Olin & Sealove, 2010).

Different techniques have been used in different studies to identify cutaneous foot temperatures such as infrared thermometry, liquid crystal thermography and infrared thermography (Lavery et al, 2007; Roback et al., 2009; Mori et al., 2013). Infrared thermometry was used by Lavery et al. (2004) to examine its use in home monitoring of foot skin temperature since it is a cheap and easily accessible tool. Their study concluded that this method could be effective in preventing diabetic foot complications in patients with high risk of amputations in the lower limb. Liquid crystal thermography is also another cheap option to record plantar temperatures however, this involves contact with the examined object and is slow compared to other methods (Lahiri et al., 2012). Infrared thermography has all the advantages of the previous two temperature monitoring devices and none of the disadvantages. This is because infrared thermography is non-contact and non-invasive technique which allows visual representation of the plantar temperature distribution.

Thermography in Predicting Diabetic Foot Ulcers

An effective way to assess the risk for diabetic foot ulcer is by using thermography (Nagase et al., 2010). A few studies have shown that an acute increase in plantar cutaneous temperature is a sign of inflammation before an ulcer appears (Lavery et al., 2007; Armstrong et al., 2007). A chronic increase in plantar cutaneous temperature can be found in patients with diabetic neuropathy mostly due to arteriovenous shunt-flow (Nagase et al., 2011). Some studies also suggest that a decrease in plantar cutaneous temperature is associated with PVD in patients with T2DM (Lavery et al., 2004; Brem et al., 2007). One disadvantage of infrared thermography is that it cannot identify the aetiology of the change in cutaneous temperatures (Hildebrandt, Raschner, and Ammer, 2010).

In a study by Lavery et al. (2004), it was established that daily monitoring of foot temperature in patients with diabetes can lead to a decrease in ulceration an amputation. The study included 85 diabetic patients with peripheral neuropathy who were randomly divided into two groups. One group of patients received standard therapy while the other group received enhanced therapy. Participants in the enhanced therapy group were instructed to measure their cutaneous temperature of the plantar aspect of the foot using in the morning and evening. An infrared

thermometer was used to measure foot temperature. A temperature difference greater than 4°F between both feet was considered of being at risk of ulceration. This led to the group with enhanced therapy to have significantly lower foot complications (2%) when compared to the standard therapy group (20%).

The use of home temperature monitoring in reducing the incidence of diabetic foot ulcers was also investigated by Armstrong et al. (2007). The study included 225 subjects with diabetes at high risk of foot ulcerations. These subjects were randomly divided into 2 groups: standard therapy group and dermal thermometry group. Participants in the dermal thermometry group used infrared skin thermometer to quantify cutaneous temperature at six different points twice daily. Subjects with a difference >4°F between contralateral limbs were instructed to contact their nurse and reduce activity. 8.4% of developed an ulcer during the study, with subjects in the dermal thermometry group (12.2%) were found to be more likely to ulcerate compared to standard therapy group (4.7%). Furthermore, the cutaneous temperature of subjects that developed an ulcer was found to be 4.8 times higher at the same spot a week prior. The study concluded that difference in cutaneous temperature between the contralateral feet may predict a neuropathic ulcer and self-temperature monitoring can reduce the risk of ulcer development.

The usefulness of monthly thermographic assessment and standard foot care in minimizing the redevelopment of diabetic foot ulcers was also investigated by Petrova et al. (2020). The study included 110 diabetic participants with neuropathy and a history of at least 1 diabetic foot ulcer. The participants were randomly assigned to either the intervention group or the control group. Both groups involved standard foot care, but the participants in the intervention group included active thermography. The participants were followed every month until a foot ulcer developed for a maximum of 12 months. When temperature $\geq$ 2.2°C difference between both feet in participants within the intervention group was detected, action was taken to prevent ulceration. Results showed that after one year, 62% of participants were ulcer free when thermography was used compared to 56% of participants in the control group. The study concluded that there was no significant reduction in ulcer recurrence when using monthly intervention with thermal camera.

In another study by Yavuz et al. (2019) foot temperatures and its role in ulcer development was investigated. The study included 37 participants which were divided into three groups based on their diagnosis. 9 subjects were diagnosed with peripheral neuropathy and have history of

diabetic foot ulcers (DFU Group), 14 subjects were diagnosed with neuropathy and do not have ulcer history (DN Group), and another 14 subjects were without peripheral neuropathy and without ulcer history used as controls (DC Group). Cutaneous temperature was recorded in four regions of interest: hallux and medial, central, and lateral forefoot. An infrared thermal camera was used to capture thermograms of the plantar aspect of the foot. The results obtained in this study showed that DFU and DN groups have a mean cutaneous temperature higher than 30^{o}C. The biggest difference in temperature was found between DFU and DC groups in the medial forefoot ROI (4.9^{o}C). The authors concluded that the increase in temperature of subjects with peripheral neuropathy and history of diabetic foot ulcer could result from one of the following:

1. acute temperature increases from plantar stresses,
2. chronic inflammation from prolonged stresses
3. impairment in temperature regulation from autonomic neuropathy.

Thermography in Identifying Peripheral Neuropathy

In 2001, Boyko et al. perform a study to analyse the cutaneous temperature of the foot in diabetic patients with sensory and autonomic neuropathy. Subjects with sensory neuropathy were diagnosed by insensitivity to 5.07 monofilament. Subjects with autonomic neuropathy were diagnosed using standard cardiovascular reflex tests. The study included 712 participants and their foot temperature was measured using an infrared surface scanner. Results showed that subjects with sensory neuropathy recorded lower mean temperatures when compared to subjects without sensory neuropathy. The study also found that autonomic neuropathy with the dichotomous variable did not influence foot temperature. However, negative correlation cutaneous foot temperature and a drop in systolic blood pressure when standing (which could be a sign of autonomic neuropathy) was observed.

According to a study by Sun et al. in 2006, diabetic patients with pre-ulcerative skin regions and no sympathetic skin response (SSR) had an average foot cutaneous temperature of 30.2^{o}C, which was significantly warmer than diabetic patients with SSR (27.1^{o}C), those without SSR (27.9^{o}C), and control subjects (26.8^{o}C) with no significant health risks.

Papanas et al. (2008) performed a study to analyse the cutaneous temperature of the foot in the presence of diabetic peripheral neuropathy. The study included 60 individuals with T2DM, 30 of which were diagnosed with peripheral neuropathy while the other 30 were without peripheral neuropathy. Diagnosis of neuropathy was done via the Diabetic Neuropathy Index. A handheld infrared thermometer was used to measure cutaneous foot temperature. Participants with peripheral neuropathy were found to have significantly higher dorsal and plantar foot temperature when compared to participants without neuropathy. Furthermore, significant positive correlation between Diabetic Neuropathy Index and foot temperature was recorded.

A study by Bagavathiappan et al. (2010) conducted a study to evaluate the cutaneous temperature of the foot in T2DM patients with peripheral neuropathy. The study included 112 subjects with T2DM. An infrared thermal camera was used to measure plantar cutaneous temperatures. Neuropathy was diagnosed by vibration perception threshold values greater than 20 V using biothesiometry. The foot was divided into six distinct areas (big toe, lesser toes, arch, lateral foot plant, forefoot, and heel), with the average cutaneous temperature calculated separately for each area. Results from the study showed that T2DM subjects with neuropathy have a higher cutaneous temperature (32^oC-35^oC) when compared to T2DM subjects without neuropathy (27^oC-30^oC). The study also found no correlation between average foot temperature and blood glucose level.

Schmidt et al. (2020) performed a study to determine normative cutaneous temperatures of the feet in patients with diabetes and peripheral neuropathy. The study included 58 participants. Results recorded mean temperatures in the toe of 27.67°C, forefoot of 28.58°C, midfoot of 29.21°C, and rearfoot of 29.88°C.

Hayashi and Shichiri (2020) used an infrared thermometer to analyse the cutaneous temperature of the feet at the 1^{st} metatarsal head, 5^{th} metatarsal head, and heel in patients with PAD. The study included 345 limbs from 176 participants. Lower temperatures were reported in patients with ABPI ≤0.90 and in patients with ultrasound-confirmed arterial stenosis. The authors also stated that high sensitivity to detect PAD can be obtained when using the lowest temperature value of the 3-foot locations. The reported sensitivity and specificity for the lowest skin temperature cut-off point of 30.8°C was found to be 60%/64%. The authors compared this to the sensitivity and specificity of ABPI cut-off point of 0.9 which shows a sensitivity and specificity of 41%/94%,

Deus Passos and Ferriera da Rocha (2022) compared the use of infrared thermography with the traditional method of doppler ultrasonography in detecting PAD above the knees (supra-popliteal PAD). The study included a total of 90 participants which were divided into two groups depending on whether PAD was present or not. The diagnosis of PAD was made using doppler ultrasonography which was later compared to infrared thermography. A difference of $2^{o}C$ or greater between two points on the same lower limb or between both lower limbs was used to diagnose PAD using thermography. The authors reported that this technique had a 97.62% sensitivity and a 91.67% specificity in detecting PAD. In addition to this, it was found that the ABPI ≤ 0.9 have a sensitivity and specificity of 91.17% and 75%.

Thermography in Identifying PAD

The use of thermography in detecting peripheral vascular disease was investigated by Bagavathiappan et al. (2009). Results from the study showed that occluded arteries lead to a decrease in temperature while inflammation and venous flow problems have resulted in 0.7-$1^{o}C$ higher temperatures.

A study by Huang et al. (2011) included 51 subjects with an average age of 70. The study had the aim to investigate the use of thermography in patients with PAD. PAD was assessed by 3 separate questionnaires: The seven-day physical activity recall questionnaire, walking impairment questionnaire, and vascular quality of life questionnaire. Segmental pressure and ABPI were used to assess PAD and level of stenosis. PAD was diagnosed by an ABPI levels of 0.9 or lower. Arterial stenosis was indicated in the limb with lowest segmental blood pressure where a segmental blood pressure drop between two limbs in the limb was present. A six-minute walking test was given as a challenge to the circulation. Temperatures of the lower limb were then recorded in a $24^{o}C$ temperature and humidity-controlled room. Cutaneous temperature was recorded before, immediately after and one minute after exercise. Cutaneous temperature was similar before six-minute walking test in both PAD and non-PAD patients. After the six-minute walking test, subjects without PAD had a slight increase or preservation of cutaneous temperature. Subjects with PAD had their sole temperature decrease significantly from $31^{O}C$ to $29.7^{O}C$. Furthermore, pattern in recovery temperature did not vary between the

two groups. The study also found a correlation between exercise induced temperature change with six-minute walking test and ABPI, which suggests that PAD severity does influence the temperature.

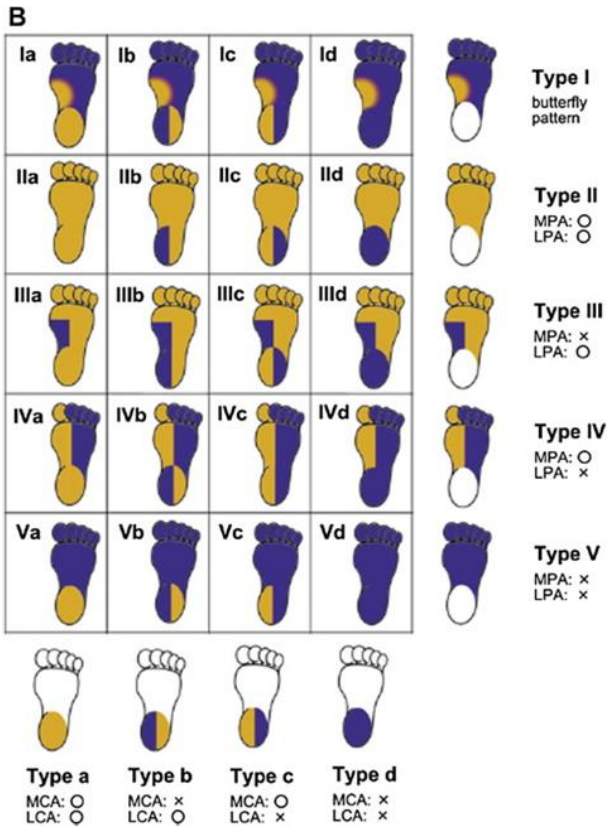

Figure 2.11: A classification system of plantar thermal patterns. Retrieved from Nagase et al. (2011)

A classification system of plantar thermal patterns based on the angiosome concept was put forward by Nagase et al. (2011). The study included 64 feet from 32 healthy control subjects. 75% of these feet (48) were classified in 7 of the 20 categories and 25% (16) were classified as atypical. The butterfly pattern was found in 46.9% of feet analysed, making it the most common category recorded. As part of the study, 258 feet belonging to diabetic subjects were examined. Of these, 87.2% fell under 18 out of 20 categories, with the remaining 12.8% being classified as atypical. The most prevalent category among diabetic patients was IIA, making up 39.1% of the cases. The authors have reached the conclusion that this classification may be overly complex for everyday use.

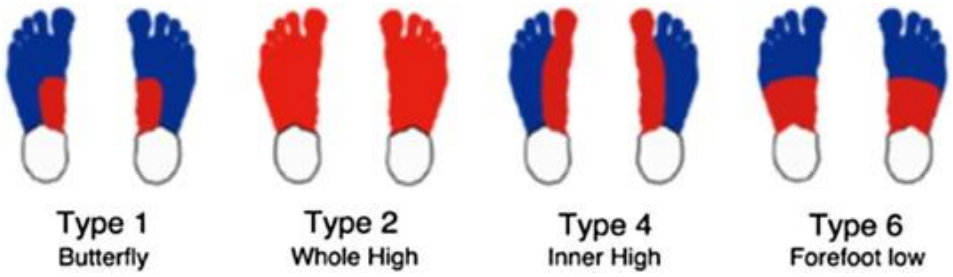

Figure 2.12: Variations of the thermographic patterns of the distal area in the non-diabetic control group. Retrieved from Mori et al. (2013)

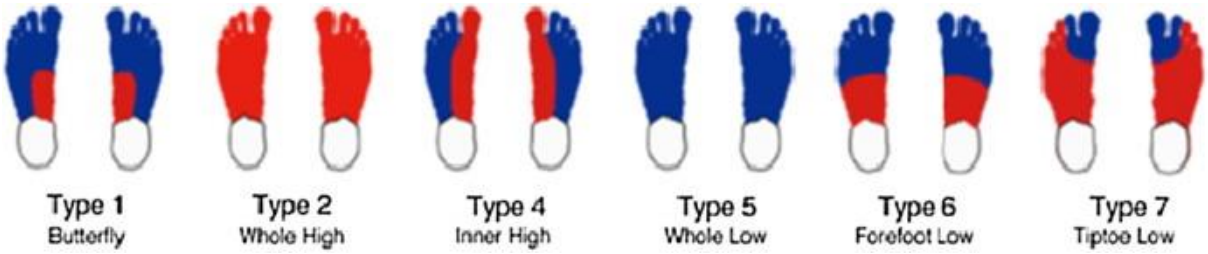

Figure 2.13: Variations of the thermographic patterns of the distal area in the diabetic group. Retrieved from Mori et al. (2013)

Another classification system for thermographic patterns by a segmentation algorithm based on a mode-seeking method was proposed by Mori et al. (2013). A total of 47 feet belonging to healthy control subjects were categorized into 4 different types, while 17 were classified as atypical. The predominant category among the healthy control group was determined to be type 1. On the other hand, diabetic subjects had 198 feet categorized into 6 types, and 60 were classified as atypical. The most frequently observed categories among diabetic feet were type 1 and type 2.

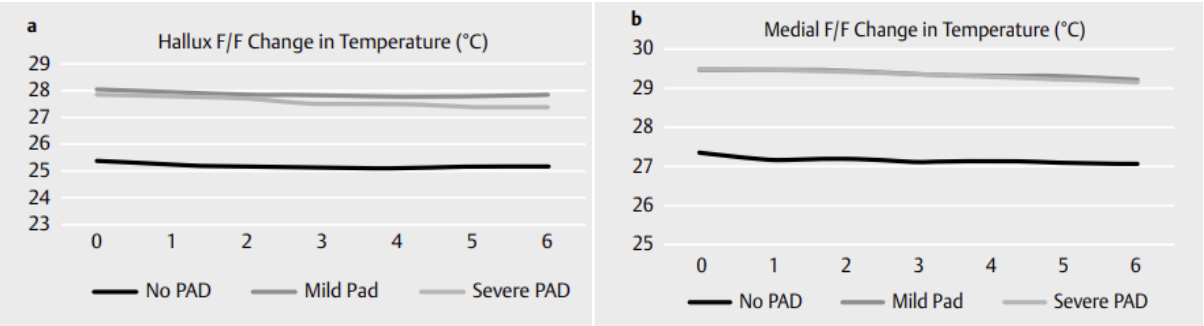

Figure 2.14: Change in foot temperature in participants with mild, moderate, and severe PAD. Retrieved from Carabott et al. (2018)

Carabott et al. (2018) performed a study with aim of comparing changes in plantar temperatures of the foot following a limb elevation challenge utilising the angiosome concept. The participants were categorized into 3 groups based on the severity of PAD. The lower limbs were elevated at a 45^{o} angle for 5 minutes and thermograms were taken every minute using a thermographic camera. The study included 42 feet from 21 participants with T2DM. Results showed that participants with PAD had higher mean resting cutaneous temperature compared to participants without PAD. The study also found that the foot elevation challenge did not significantly affect the thermal pattern.

Thermography in Identifying T2DM Foot Complications

Symmetry between contralateral limbs is associated with healthy subjects while asymmetry of cutaneous temperature distribution could be an indicator of abnormality. A study conducted by Van Netten et al. (2014) aimed to explore the use of different cutaneous temperature cut-offs in identifying foot complications related to diabetes, such as ulceration, infections, and Charcot foot. The study involved 54 participants with diabetes, who were categorized into three groups. One group required immediate treatment for their complications, another required non-immediate treatment, and the last group had no complications requiring treatment. The study revealed that a 2.2^{o}C difference between contralateral spots could be used to identify diabetic complications, with a sensitivity of 76% and specificity of 40%. Additionally, a 1.35^{o}C difference between contralateral limbs is considered to be optimal in determining the urgency of treatment, with a 89% sensitivity and 78% specificity.

Ilo et al. (2020) examined the diagnostic potential of infrared thermography compared to other conventional non-invasive methods. One hundred eighteen participants with diabetes and 93 healthy participants were included in the study. ABPI and toe pressure index were used to diagnose PAD. Results showed that participants with diabetes have warmer feet compared to healthy participants. Furthermore, the mean cutaneous temperature difference between both feet was also found to be greater in participants with diabetes.

Serantoni et al. (2020) performed a study to assess the use of a thermal camera in characterising thermoregulatory mechanisms in the feet depending on the lower limb diabetes complication (peripheral neuropathy, PAD and neuroischaemia). The study included 51 participants (8 participants without diabetes and 43 participants with diabetes). Ten participants were diagnosed with peripheral neuropathy, four with PAD and eight with neuroischaemia. The study involved the participants staying in a semi-fowler position for 5 minutes at a temperature of 25^{o}C. A ten-minute thermal recording of the plantar aspect of the foot was done, followed by a six-minute walking test and another ten minutes thermal recording of the foot. The study found that poor differences were recorded before the six-minute walking test, and therefore it is important for the thermoregulation mechanism to be activated before any interpretation. The study also found that it is possible to identify diabetic foot complications and their severity in participants with diabetes due to alteration of thermoregulatory mechanism amplitude.

A study by Gatt et al. (2018) had the aim to evaluate the potential of thermography as an assessment tool to detect T2DM foot complications based on variations in plantar cutaneous temperatures. The study included 289 limbs from 182 participants. All participants were tested for PAD and peripheral neuropathy using medically validated tests. These tests consisted of ABPI, doppler waveform and 10g monofilament. An ABPI of less than 0.6 and a monophasic Doppler waveform were used to diagnose PAD. Neuropathy was diagnosed by not feeling the 10g-monofilament and a reduced vibration sensation by a 128Hz tuning fork. Based on the results from the medical examination, the participants were divided into five groups, including one group with healthy participants without T2DM. The other four groups consisted of a healthy T2DM group, a PAD group, a neuropathic group, and a neuroischaemic group. The study was carried out in a temperature-controlled environment of 23^{o}C. Participants were first rested in a supine position for 15 minutes and medically validated tests for PAD and neuropathy were carried out.

The study found that there is no significant difference in mean temperatures of forefoot and toes between healthy adults and DM participants with no complications. No significant difference in mean temperatures was also found between groups of PAD, neuropathy and neuroischaemia. However, results also showed that there is a statistically significant difference in mean cutaneous temperatures between the two healthy groups and the 3 DM complications groups. Furthermore, the mean cutaneous temperatures in T2DM groups with foot

complications (PAD, neuropathy and neuroischaemia) are significantly warmer when compared to cutaneous temperatures in healthy adults and T2DM without complications.

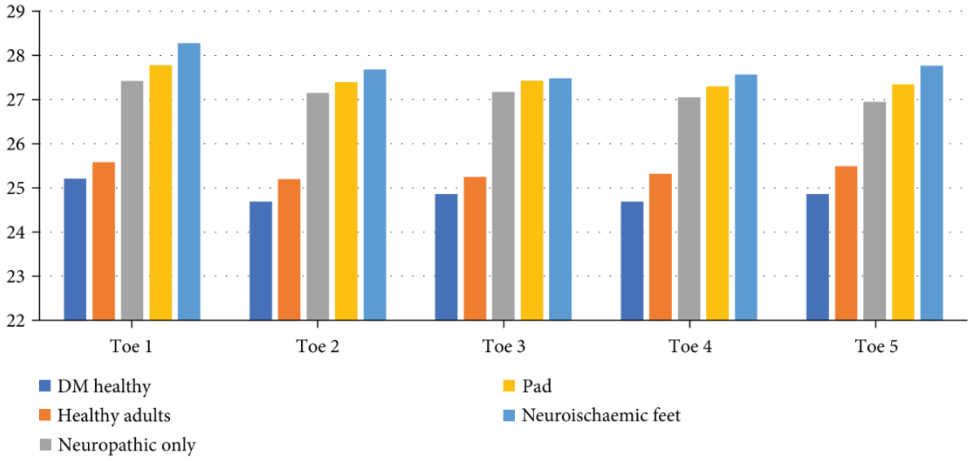

Figure 2.15: Mean toe temperatures. Retrieved from Gatt et al., 2018

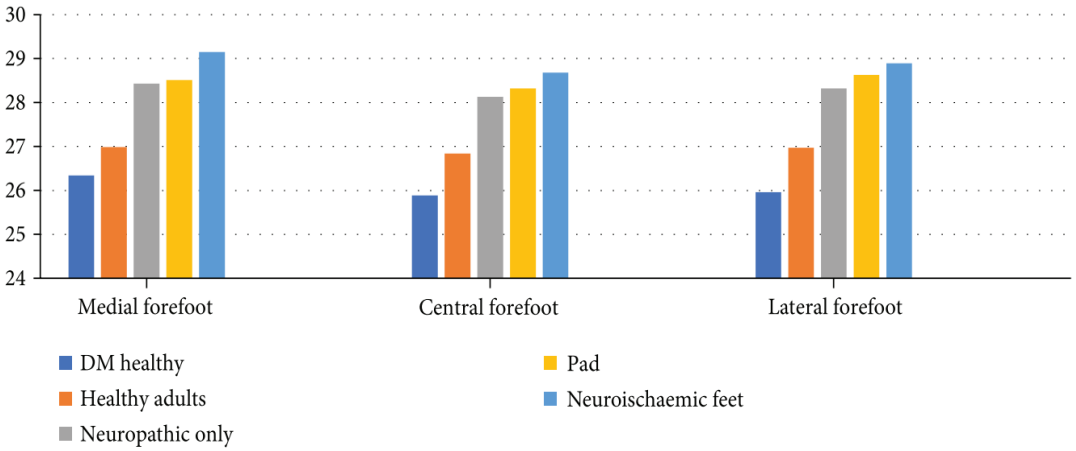

Figure 2.16:Mean forefoot temperatures. Retrieved from Gatt et al., 2018

Logistic regression analysis was carried out to determine the probability that diabetic foot complications are present and the probability that the patient is healthy based on mean cutaneous temperature of the toes and forefoot.

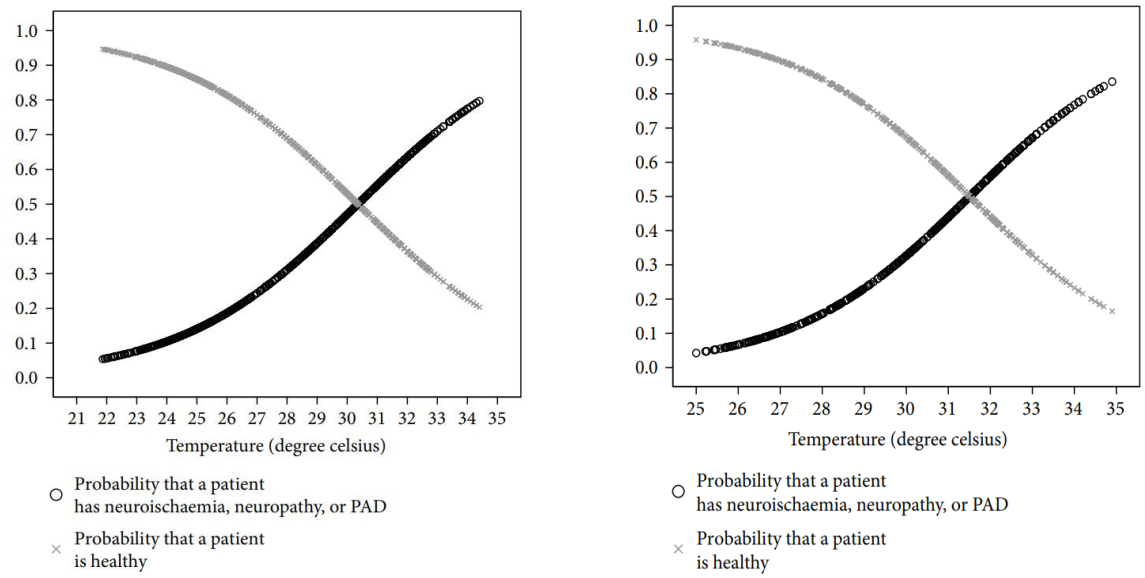

Figure 2.17:Logistical regression curve of forefoot (left) and toe (right) temperatures. Retrieved from Gatt et al. (2018)

Results from this study showed that for every 1ºC increase in mean temperature of toes, there is a 24.7% increase in probability that diabetic complications are present instead of being healthy. In the forefoot, the probability that diabetic complications are present instead of being healthy increases by 28.9% for every 1ºC increase in mean temperature. Logistic regression curves for forefoot temperatures and toe temperatures can be seen in figure 2.14. Hence, the results from this study suggest that an increase does not only occur before an ulcer appears, as reported by Sun et al. (2006), but also when diabetic complications (PAD, neuropathy, or ischaemia) are present. From the logistic regression curves, the authors produced an equation that can be used to determine the probability of presence of complications using cutaneous temperature. Two separate equations were produced, one for the forefoot (Figure 1.2) and one for the toes (Figure 1.1).

Several studies have already shown that neuropathy leads to an increase in temperature, however, this study also suggests that an increase in temperature is also present with PAD and neuroischaemia. The reasons for this increase in temperature are still unknown, however, Gatt et al. (2017) suggest that this could be due to the modified thermoregulatory mechanism of the feet. Complications with the sympathetically mediated noradrenergic vasoconstriction due to ischaemia may lead to more blood flow through cutaneous arteries rather than deep arteries which results in higher cutaneous temperatures.

Conclusion

With the increasing number of diabetic patients worldwide and the high risk of developing foot complications associated with this disease, there is a growing need for amalgamating alternative technologies to increase the speed and efficiency of diabetic foot screening.

It is important for individuals with diabetes to undergo regular foot examinations to prevent ulcers and factors that increase the risk of amputation. The American Diabetes Association recommends a comprehensive foot assessment at least once a year (ADA, 2018).

Studies investigating foot temperature have shown promising results that can lead to incorporating temperature monitoring devices to diagnose diabetic foot disease or monitoring of the diabetic foot. This literature review showed that different studies had recorded different results, leading to different conclusions regarding the use of temperature monitoring devices and their use in diagnosing diabetic foot disease. Most research does agree that patients with neuropathy tend to have higher cutaneous foot temperatures; however, there are disagreements between different research involving temperature change in patients with PAD.

Building on research done by Gatt et al. (2018), which demonstrated a significant increase in foot temperature in patients with T2DM foot complications, this study will aim at determining whether an infrared thermographic camera can be used to detect these foot complications. This will be done by using equations that determine the probability of complications present based on the cutaneous temperature of the foot. Sensitivity, specificity, negative predicted value, and positive predictive value of this method will be provided for every ROI. The Sensitivity, specificity, negative predictive value, and positive predictive value will be discussed in Chapter 3, including the importance, advantages, and disadvantages of these measurements.

Chapter 3 : Method & Methodology

Introduction

This chapter has the aim of giving a thorough explanation of the method and methodology used in this research. This will include details on how the data was collected, managed, and analysed to extract the results and draw the necessary conclusions.

A clear method and methodology are crucial because these provide a structured approach to research and ensure that the study is carried out in a systematic and rigorous manner. Using a well-defined method, researchers can gather and analyse data in a standardised way, which aids in providing accurate data (Goundar, 2012). Therefore, this helps to increase the credibility and trustworthiness of the research findings.

The methodology is also important because it ensures the research is carefully planned and well-executed. A carefully constructed methodology guides the researcher in selecting the appropriate research design and methods, which helps to reduce errors, biases, and confounding factors that could affect the reliability and validity of the study. Additionally, the methodology provides a structure for examining and interpreting the results, ensuring the data's conclusions are solid and supported (O'Leary, 2007).

The research problem is an issue that needs to be addressed by asking the research question and identifying the aim of the research. This research investigated whether thermography could be used to identify T2DM foot complications. Data collected included separate cutaneous temperatures from eight ROIs in the plantar aspect of all the toes, 1st MTH, 3rd MTH, and 5th MTH, as seen in Figure 3.6. Diagnostic tests for PAD and neuropathy consisted of Doppler ultrasound, ABPI, 10g-monofilament, and 1288 MHz tuning fork testing by a qualified clinician blinded to the thermography testing results.

Research Design

The research design refers to the plan, structure and strategy used to conduct a research study (Kerlinger, 1986). The research design consists of the structure for the entire research, from the research question to the presentation of results. It outlines the procedures, methods, and techniques used to collect and analyse data and how the results were interpreted and reported (Wang & Kattan, 2020).

A carefully planned research design is important because it helps ensure that the study is conducted rigorously and systematically and that the results are valid and reliable. Furthermore, Jongbo (2014) states that if the data is collected before constructing a good research design and identifying what data is needed to answer the research question, the conclusions from the research are likely to be weak and unconvincing, leading to failure in achieving the research objectives. The research design should be tailored to the research question being investigated and based on established research methods and techniques (Crotty, 1998).

Robson (2011) stated that there are three forms of research design depending on the purpose of the research: exploratory, descriptive and explanatory. A descriptive study aims to explain an event or describe the relationship between variables (Blumberg, Cooper and Schindler, 2005). This form of research design is most suitable for new research as it cannot describe how an event occurred (Punch, 2014). Exploratory research is carried out when not enough is known about a particular subject and the problem has not been clarified (Saunders et al., 2007). The aim of exploratory research is to address problems on which there has been very little to no prior research conducted. (Brown, 2006). Explanatory research aims to explain the descriptive data. Contrary to descriptive research, which does not explain how an event occurs, explanatory research aims to explain why and how an event occurs (Grey, 2014).

This research aimed to determine whether thermography can identify T2DM foot complications. This was achieved through a quantitative approach using mathematical and statistical tools. The aim was not to explain how and why this event occurs but rather to describe the relationship between the probability of T2DM foot complications and the actual presence of T2DM foot complications. Therefore, this research can be classified as a form of descriptive research.

Components of Research Design

The research design refers to the plan of how the research will be conducted and how the research question will be answered (Grey, 2014). There are three components that one must take into consideration when choosing a research design:

1. Philosophical Paradigms
2. Strategies of Inquiry
3. Research Method (Creswell, 2009)

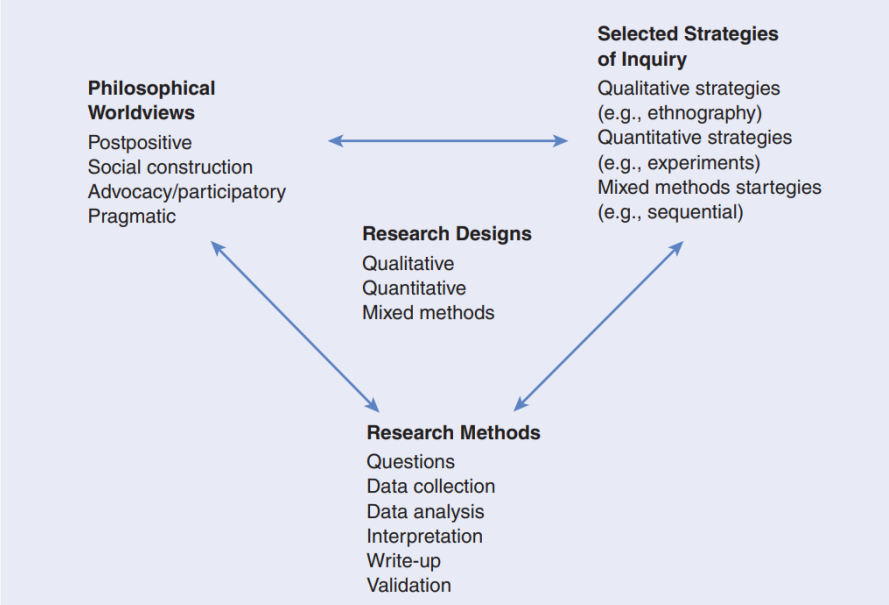

Figure 3.1:Components of Research Design. Retrieved from Creswell (2009)

Philosophical Paradigms

In order to navigate scientific discoveries based on their assumptions and principles, it is important to have a solid grasp of research philosophical paradigms (Park, Konge, and Artino, 2020). The elements of research paradigms help to understand and formulate beliefs about reality, what can be known about it and how to achieve this knowledge (Rehman & Alharthi, 2016).

According to Lincoln and Guba (1985), a philosophical paradigm is made up of:

- the researcher's beliefs about how an investigation should be performed (methodology)
- the researcher's definition of truth and reality (ontology)
- how the researcher discovers the truth or reality (epistemology)

Therefore, the philosophical assumptions about ontology and epistemology will influence the methodological choice of a researcher (Collis and Hussey, 2003).

Understanding and selecting an appropriate philosophical paradigm is crucial to conducting meaningful and rigorous research. The philosophical paradigms will influence the researcher to choose one of the three strategies of inquiry. The four most common research paradigms are:

1. Postpositive
2. Social Construction
3. Advocacy/Participatory
4. Pragmatic

Postpositivism	**Constructivism**
• Determination • Reductionism • Empirical observation and measurement • Theory verification	• Understanding • Multiple participant meanings • Social and historical construction • Theory generation
Advocacy/Participatory	**Pragmatism**
• Political • Empowerment Issue-oriented • Collaborative • Change-oriented	• Consequences of actions • Problem-centered • Pluralistic • Real-world practice oriented

Figure 3.2:Philosophical Paradigms. Retrieved from Creswell (2009)

Post-positivist Paradigm

The ontological position of positivists is that of realism, and the epistemological position is that of objectivism. The positivist approach has been heavily criticised by scholars due to its lack of success when applied to social phenomena. This criticism of the positivist paradigm led to the emergence of post-positivism (Fox, 2008). This new post-positivism paradigm incorporates both the positivist and interpretivism paradigms with the aim of addressing the weaknesses of the positivist paradigm (Grix, 2010). This paradigm is often known as the scientific method. The ontological position of post-positivism is that of critical realism. It acknowledges the existence of an objective reality but recognises that our understanding of it is limited by our subjective experiences and perceptions (Cresswell, 2009).

Post-positivism was chosen for this research as it assumes that scientific knowledge can be acquired through empirical observation and measurement and that this knowledge is always tentative and subject to revision based on new evidence. Furthermore, the post-positive research paradigm uses various research methods, including the quantitative approach used in this research, to gain a more complete understanding of complex phenomena (Fox, 2008).

Social Constructivist Paradigm

Social constructivism is often described as interpretivism. It is a philosophical paradigm in social sciences that seek to understand the world by emphasizing the role of social, cultural, and historical context in shaping human experience and behaviour (Creswell, 2013; Denzin & Lincoln, 2011). Social constructivists interpret their world through a subjective lens which is guided by epistemological, axiological, and ontological positions that formulate their personal reality. This philosophical paradigm was not ideal for this research as it typically uses qualitative approaches, such as ethnography, participant observation, and interviews, to gain an in-depth understanding of social phenomena from the participants' perspective.

Advocacy and Participatory Paradigm

An advocacy/participatory philosophical paradigm holds that research questions need to relate to politics and a political agenda. Therefore, the research contains an agenda for reform that may change the researcher's or participant's lives (Creswell, 2009). This research paradigms prioritise the involvement of marginalised communities in the research process. This approach aims to empower communities to take an active role in identifying research questions, designing research projects, collecting and analysing data, and disseminating findings. This research paradigm is often associated with qualitative research but can also be the basis of qualitative research (Creswell, 2009). This philosophical paradigm was not chosen for this research as it does not relate to politics and political agenda in marginalised communities.

Pragmatic Paradigm

Pragmatism is a research paradigm that emphasizes the practical consequences of research findings and their usefulness in solving real-world problems. According to Creswell (2009), this research paradigm differs from post-positivism because it arises from actions, situations, and consequences rather than antecedent conditions. In contrast to other research paradigms that prioritise theoretical or methodological purity, pragmatism is focused on the practical application of research findings to improve people's lives.

Pragmatic research typically uses mixed methods approaches, combining qualitative and quantitative methods to answer research questions (Morgan, 2007). Therefore, this philosophical paradigm was not applicable in this research since only the quantitative approach was used to answer the research question.

Strategies of Inquiry

This refers to the type of study within one of the three research designs: qualitative, quantitative, or mixed methods. Strategies of inquiry are systematic and structured approaches used to investigate a research problem or question. Within a research design, the strategies of inquiry aid in providing specific direction.

Teddlie & Tashakkori (2009) explain that there are three types of research approaches: qualitative, quantitative, and mixed methods. Since this research involves collecting and analysing quantitative data using statistical and mathematical tools to derive results, the quantitative approach was deemed the most suitable to address the research question.

The choice of the research design should not be made randomly; however, it should depend on the type of the research to be carried out. Choosing the correct research design enhances the probability of successful research. The aim of the research design is to attain the research objectives and produce reliable and valid results by controlling extraneous variances and minimising errors. A research gap is identified by analysing the current literature on a particular subject of interest. This research gap is then critically analysed and formulated into a research question with the desired objectives (Asenahabi, 2019). The most appropriate and relevant research design is selected by having proper knowledge of the research designs, analysis of the research question, theoretical framework, and current literature (Asenahabi, 2019).

Quantitative Research

Quantitative research design is a type of research methodology that produces quantifiable values (Kothari, 2007). It involves collecting and examining numerical data, which is analysed using statistical or mathematical tools to provide empirical evidence that answers the research question (Aliaga and Gunderson, 2000). This research method is based on the postpositivist philosophical paradigm (Phillips & Burbules, 2000).

The greatest advantage of using a quantitative research approach is the potential to generalise to a large population due to reliable and quantifiable data produced (Marshall, 1996). In this research, the quantitative approach was used to answer the research question as follows:

"What is the sensitivity and specificity of thermography in predicting the presence of T2DM foot complications of Peripheral Arterial Disease, Neuropathy and Neuroischaemia?"

As seen in the literature review, recent research by Gatt et al. (2018) revealed logistic regression models that show a relationship between T2DM foot complications and plantar foot temperature. Gatt et al. (2018) also produced equations to determine the probability that persons with T2DM have diabetic foot complications using thermography to determine cutaneous temperature. This study will use these mathematical equations to determine the probability of T2DM foot complications in all the participants while also using statistical tools to determine the sensitivity, specificity, negative predictive value and positive predictive value of thermography to identify T2DM foot complications.

Quantitative research can be divided into experimental or non-experimental research designs. Non-experimental research does not involve the manipulation of variables in the process of data collection. This research can be considered non-experimental since it involves the measurement of plantar foot temperatures with no manipulation of variables (such as ambient temperature).

Non-experimental research is further divided into three groups: survey design, casual-comparative design, and correlation design. Surveys are often used to collect data such as opinions, attitudes, and trends using close-ended questions from a large sample of participants, allowing researchers to generalise findings to a larger population (McNeill and Chapman, 2005). Causal-comparative quantitative research, also known as ex post facto research, is a type of quantitative research design used to investigate the relationship between two or more variables concerning a cause that has already occurred (Creswell, 2013). Correlational research involves analysing the degree of association between two or more variables to determine if there is a correlation between them by using correlational statistics (Creswell, 2013). In this research, the probability of T2DM foot complications was correlated with the actual presence or exclusion of T2DM foot complications to determine the sensitivity and specificity. Therefore, this research can also be considered as correlational research.

Experimental research involves the manipulation of at least one dependent variable to measure the cause-and-effect relationship on the selected subject matter (Jongbo, 2014). Most commonly, experimental research involves a control group and an experimental group where the experimental group is manipulated and the control group is not. This enables the researcher to determine the type of the connection between the variables investigated. There are a number of different experimental research designs, such as pre-experimental, quasi-experimental, and true-experimental designs. Pre-experimental design is when the researcher investigates the effect of an intervention applied during the study on a single group. In quasi-experimental research, there are both control and experimental groups; however, participants are not randomly assigned to these groups. When participants are randomly assigned to these groups, it is referred to as a true-experimental research design (Asenahabi, 2019). This research did not involve any manipulation of variables, and therefore it is not considered experimental research.

Qualitative Research

Qualitative research is a type of research methodology that focuses on gathering unquantifiable data through open-ended, unstructured, and exploratory questions (Asenahabi, 2019). This provides a way of understanding a phenomenon by observing or interacting with the participants (Denzin & Lincoln, 2008). This is done through approaches such as interviews, observations, focus groups, case studies, and document analysis. The aim of qualitative research is to understand human behaviours, beliefs, and attitudes through the opinions and experiences of participants (Merriam & Tisdell, 2017).

This type of research is particularly useful when the research question is exploratory and the researcher seeks to gain a deeper understanding of the topic or phenomenon being studied. The qualitative research method is based on the constructivist philosophical paradigm (Lincoln et al., 2011).

The qualitative research design was not ideal for this study since it relies on subjective interpretations, inductive reasoning, and descriptive analysis to produce data that is often rich in detail and can provide insights into complex phenomena that cannot be easily quantified (Creswell, 2003). This study involved the collection of numerical quantifiable data such as

plantar foot temperature and probability of T2DM foot complications in determining whether thermography can be used to identify T2DM foot complications using statistical tools to determine the sensitivity, specificity, positive predictive value and negative predictive value for every ROI and probability cut-off point.

Mixed Research

Mixed methods research is a research approach that integrates both qualitative and quantitative research methods together in a single study (Hanson et al., 2005). Mixed methods research is used when the research question cannot be answered using either quantitative or qualitative methods separately. The aim of mixed methods research is to provide a broader purpose of breadth and depth of understanding of a research problem by combining the strengths of both qualitative and quantitative methods (Burke-Johnson et al., 2007). Mixed methods research typically involves collecting and examining qualitative and quantitative data and then meaningfully integrating the results. This research approach is based on the pragmatic philosophical paradigm (Tashakkori & Teddlie, 2010).

Prospective vs Retrospective research

In prospective research, recruited participants are assessed at the start of the study and followed up over a period of time to investigate changes in certain data (such as disease development or mortality), as seen in Figure 3.3. Major advantage of prospective research is the accuracy of data collection; however, this is both expensive and time-consuming (Euser et al., 2009).

In retrospective research, the study starts when the follow-up has been completed, and the data collected is based on the participant's history (Euser et al., 2009). Retrospective research involves forming a cohort and assessing the exposures at baseline. This study involved the assessment of plantar foot temperature, PAD and neuropathy at baseline in an exposed group (participants with T2DM foot complications) and an unexposed group (participants without T2DM foot complications). Therefore, it can be considered as a retrospective study.

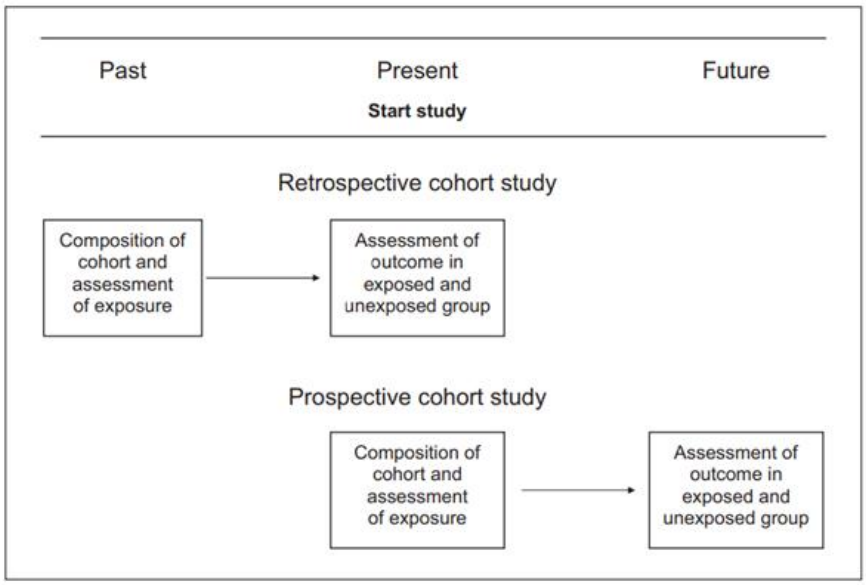

Figure 3.3:timelines of retrospective and prospective research. Retrieved from (Euser et al., 2009).

Sampling

The collection of data to answer the research question can prove to be a challenging task for the researcher; therefore, it is important to be knowledgeable about the different and most appropriate sampling techniques for the specific research (Rahman et al., 2022).

Due to time and resources, it is impossible for a researcher to collect data from the total population to answer a research question. The primary goal of sampling is to obtain a sample representative of the total population. This will enable the researcher to make valid generalisations about the populations based on data collected from the sample. Samples provide a time- and cost-efficient way of conducting research (Rahman et al., 2022).

Kadam & Bhalerao (2010) described three levels of sampling. These are population, target population and sample population. Population pertains to the whole community under study, e.g., patients with T2DM. Target population refers to the subset of the population determined by a study's inclusion and exclusion criteria. Sample population refers to a group of the target population representing the total population being researched in the study (Kadam & Bhalerao, 2010).

Sampling Techniques

When the sample size is large, sampling is important to get accurate results (Bhardwaj, 2019). Sampling techniques can be divided into two categories (Elfil and Negida, 2017; Shorten, and Moorley, 2014).

- Random sampling techniques
- Non-random sampling techniques

Random sampling techniques

This technique involves selecting individuals from a population so that each member has the same probability of being selected. Using this technique increases the likelihood that the sample accurately reflects the population, and minimizes the potential for sampling bias. (Curtin et al., 2005; Fowler, 2009).

Some common random sampling techniques include simple random, stratified, and cluster sampling. Simple random sampling involves randomly selecting individuals from the population; therefore, every participant has the same likehood of being included in the sample. Stratified random sampling involves dividing the population into strata based on certain characteristics and randomly selecting a sample from each stratum. This type of sampling is commonly used when there is a high degree of variation within the population. Cluster sampling involves the population being divided into several groups or clusters. Then a random sample is selected from these clusters, all used in the final sample (Wilson, 2010). Due to time and money-saving advantages, this sampling technique is often used when researching subjects scattered over a large geographical area.

Non-random sampling techniques

Non-random sampling techniques do not involve the random selection of individuals from the population; therefore, not every member of the population has the same chance of being selected. Sometimes these techniques may be less reliable than random sampling techniques, as they can lead to sampling bias. However, certain situations may be ideal for these sampling techniques (Taherdoost, 2016).

Some common non-random sampling techniques include convenience, purposive and quota sampling. Convenience sampling involves selecting individuals who are easily accessible or readily available. This is often used in situations where it is difficult to obtain a random sample. Purposive sampling involves selecting individuals based on specific criteria relevant to the research question. This is often used in qualitative research or when the researcher is interested in studying a specific group of individuals. Quota sampling involves selecting individuals based on predetermined quotas for certain characteristics, such as age or gender. This is often used in market research or public opinion polling. The choice of sampling technique will depend on the research question, the population being studied, and practical considerations such as time and resources (Taherdoost, 2016).

Convenient Sampling

Convenience Sampling was used in this research. This type of non-probability sampling is a low-cost and easy technique where individuals most accessible to the researcher are recruited (Etikan et al., 2016). In this case, T2DM patients who attend Malta's healthcare centres were recruited with an intermediary's help. This sampling technique has the disadvantage of leaving out many potential participants who are not contacted, which could decrease the accuracy of the data collected. Outliers and bias are other disadvantages of convenient sampling that could affect research results (Etikan et al., 2016).

Sample Size

Determining the appropriate sample size in research is very important. This is because if the sample size is too small, it may not indicate the total population, and results will be deemed inaccurate. On the other hand, a sample that is too big can be impractical as it can significantly increase the cost and time to perform the research (Suresh &Chandrashekara, 2012).

A designated sample size of 100 participants was selected for this research. However, the final sample size was 32 participants (64 feet). This was mostly due to the covid pandemic because most eligible participants declined to participate in the study since they fall within the high-risk category. Other reasons for the small sample size were patients with T2DM that did not fit the inclusion/exclusion criteria and potential participants that agreed to participate in the study but did not show up at the time of the appointment.

Ethical Considerations

Ethical considerations are an important aspect of research design and should be considered throughout the research process. Ethical considerations in research refer to the principles and standards of conduct that guide researchers to ensure that the study is conducted in a morally responsible manner and respects the rights and dignity of the participants (Crowe et al., 2011).

Informed consent:

This is a process in which a potential research participant is informed about key facts about the research, including any potential risks and benefits, before deciding whether to participate in the research or not. For informed consent to be valid, this must be given by a competent person on a voluntary basis (Nnebue, 2010). Basic elements of informed consent include the following.

- identity of the researchers, the purpose of the research,
- procedure of the research,
- identity of other individuals associated with the research,

- reasons why the participant was selected,
- any potential harms and benefits,
- details about anonymity and confidentiality,
- any potential future use of the data collected,
- right not to participate or withdraw from the research. (Nnebue, 2010).

Furthermore, potential participants should be given enough time to digest the information given before deciding to participate in the research.

The intermediary, a podiatrist working within the primary health care setting, approached eligible persons. The potential participants were fully informed about the research study, its purpose, potential risks and benefits, and their rights as participants by the intermediary. The intermediary asked participants who fit the inclusion and exclusion criteria to participate in this research. Every participant willing to participate in this research was requested to sign a consent form. An information sheet containing all the information of the research was given to the participants by the intermediary for them to keep. Both the information sheet and the consent form were available in Maltese and English languages (Appendices 6-9). Participants were encouraged to ask questions that they might have had regarding their involvement in this research. The participants were notified that they had the freedom to pull out of the study at any point in time without providing any explanation.

Privacy and confidentiality:

Participant's personal information was kept confidential and only used for research purposes. Necessary steps were taken to protect participant's privacy and confidentiality throughout the study. To provide anonymity, every participant was given a code number upon signing the consent form. Thermograms of the plantar aspect of the feet that were collected were stored on a computer protected by a password known only to the researcher. The images taken did not include visual images but only thermal images of the soles of the feet. Temperature data from these thermal images were recorded.

Participation was pseudonymised, meaning all data was anonymous to the people who held/ received it. All personal data was kept completely confidential using only a code number and

put into a computer protected by a password known only to the researcher. In addition, once the research is completed, all personal data will be permanently deleted.

Conflict of interest:

This refers to situations that risk professional judgement or actions regarding a primary interest being inappropriately influenced by a secondary interest. These secondary interests are often of financial nature; however, other interests can also be present such as to advance in a professional career. Research outcome can be affected if the researcher`s decisions are based on achieving these secondary interests leading to a conflict of interest (Dhingra, 2021). There were no conflicts of interest that could potentially affect the study's outcomes or interpretation.

Ethical Approval

Ethical approval for this research was obtained from Faculty Research Ethics Committee (FREC) and University Research Ethics Committee (UREC). A copy of the FREC approval form may be found in Appendix 1.

The following permissions were obtained to carry out the data collection.

- Permission from the Lead of Podiatry and the Data Protection Officer for recruitment of patients from Podiatry Clinics at the Primary Health Care Centres in Malta.
- Permission from the Head of the Podiatry Department at the Faculty of Health Sciences to use the FLIR Thermographic Camera in the Podiatry Department and Podiatric biomechanics laboratory.
- Permission from the intermediary Podiatrist to identify and approach patients matching this dissertation's inclusion and exclusion criteria.
- Signed consent form from every participant participating in this study.

Research Methods

Recruitment of Participants

To provide accurate information, the sample size for a study should be large enough to include different aspects of the population (Zamboni, 2017). For the purposes of this study, it was necessary to have a sufficiently large sample size in order to guarantee a randomly selected group of subjects with a variety of characteristics, including those without diabetic foot disease, neuropathy, ischaemia, and neuroischaemia.

The Podiatric biomechanics laboratory within the Faculty of Health Sciences at Mater Dei Hospital was used to conduct this research. Sixty-four feet from 32 participants were selected with the help of an intermediary based on a set of inclusion and exclusion criteria (Table 3.1). The intermediary recruited all participants from the Podiatry Clinics at the Primary Health Care Centres around Malta.

The participants were given a detailed overview of what the research involved, their role in this study and what would happen to the data collected once the research was completed. An information sheet including all the details was given to every participant for them to keep. Furthermore, every participant had to sign a consent form showing their willingness to participate in this research. The study was carried out in accordance with the Declaration of Helsinki as revised in 2000 (World Medical Association, 2013). Data collection took place between June 2021 and February 2022.

For privacy purposes, each participant was assigned a unique appointment to visit the biomechanics lab. To ensure accurate thermographic examination results, participants were advised to avoid wearing tight clothing and applying any lotions, creams, or powders on their feet on the day of the appointment. The participants were also advised not to bathe one hour before the appointment.

Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
T2DM patients, as per WHO diagnostic criteria	Non-T2DM patients
18 years or older	<18 years of age
Both males and females	
Absence of active foot ulcers	Presence of active foot ulcers
Signed informed consent	Unable to provide informed consent
No history of angioplasty or lower extremity bypass surgery	History of angioplasty or lower extremity bypass surgery
	Other significant co-morbidities that may influence cutaneous temperatures, such as rheumatoid arthritis or Raynaud's phenomenon

Table 3.3:1:Inclusion/Exclusion Criteria

Data Collection

Prior to data collection, an assessment sheet (Appendix 10) was constructed to record all the necessary data in a timely and organised manner. Data collected before capturing the thermal images included the code of the participant, age and gender. Data in the data sheet that was filled in after capturing the thermal images included information such as image number. Another podiatrist was tasked to collect data to which the researcher was blinded, and this consisted of Doppler waveform, ABPI, 10g-monofilament, and 128Hz Tuning fork, which was also recorded in the assessment sheet.

The Set-up and Start of Research

Before the participants entered the lab, the temperature was set to 23ºC because it is known that ambient temperature can affect skin temperature and therefore, it is important to maintain a consistent temperature for all participants. (Foltyński et al., 2014). This was also done to maintain conformity with published research as Gatt et al. (2018) also performed their study in these conditions; this would allow comparison of results. The Brannan Wireless Thermometer was used to measure the ambient temperature to ensure that the 23ºC inside the lab was always kept constant. The FLIR T630sc infrared camera was placed perpendicular and 1.5m away from the foot using a tripod, as seen in Figure 3.4, as per the study by Gatt et al., 2018 which also followed the protocols of the American Academy of Thermology (Bharara et al., 2006). A mark on the floor was made to ensure that the couch and tripod were paced at exactly the same place for each participant to improve the accuracy of the research.

Figure 3.4: Setup

Participants laid on the couch in the supine position for 15 minutes as advised by previous literature (Marins et al., 2014; International Academy of Clinical Thermology, 2002;) for the body to equilibrate with ambient conditions of the laboratory. During the 15-minute waiting time to capture thermographic images, the participants were given another brief description of what the research entailed and their rights as participants. Furthermore, general demographic data (as described in the previous section) was asked and recorded on the data collection sheet.

Before capturing the thermographic image, it was made sure that the camera was well calibrated and working properly. The camera was fully calibrated before the commencement of the research. A black screen was applied behind the feet to enhance the visibility of the feet being studied by eliminating unwanted background thermal data. A thermogram of the plantar aspect of the feet was then taken by the researcher, without knowing whether each participant had diabetic foot diseas. Recommendations from the American Academy of Thermography were followed when capturing thermographic images (Bharara et al., 2006). Each thermographic image was named with the code of the respective participant and saved on a password-protected laptop known only to the researcher.

Flir T630 Thermal Camera

A FLIR T630sc infrared camera was used to capture thermographic images in this study. This camera has a spatial resolution of 640 × 480, a spectral range of 7.5–13µm, temperature sensitivity within 0.04 m-Kelvin, a maximum image capture rate at full resolution of 30fps, and a temperature resolution of 20 mK. The range of temperatures that this thermal camera can detect is between -40° to 650°C. The thermograms were taken following the advice of the American Academy of Thermography.

Figure 3.5: Flir T630 Thermal Camera

Extraction of Thermographic Data

The thermographic image produced by the thermographic camera was then analysed using specialised software. FLIR Research IR was used to determine the mean cutaneous temperatures of specific areas of the plantar aspect of the foot. FLIR research IR is a software that allows the researcher to identify regions of interest (ROI) on the thermal image to record data specific to the selected region. This is done by the manual setup of the ROIs using polygons and ellipses, as seen in Figure 3.7.

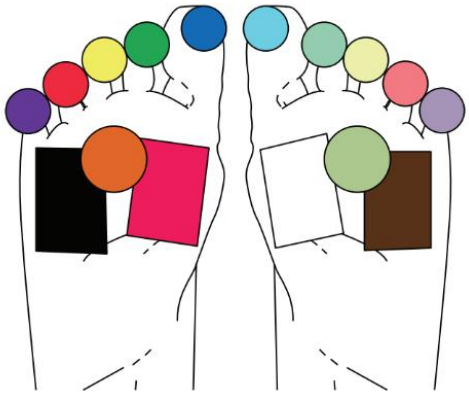

Figure 3.6: Regions of Interest. Retrieved from Gatt et al. (2018)

The areas used for this study were based on the study by Gatt et al. (2018), in which eight specific ROIs were used (Figure 3.6). The areas of the foot in which the mean temperature was recorded consisted of the hallux, 2nd toe, 3rd toe, 4th toe, 5th toe, 1st MTH, 3rd MTH and 5th MTH.

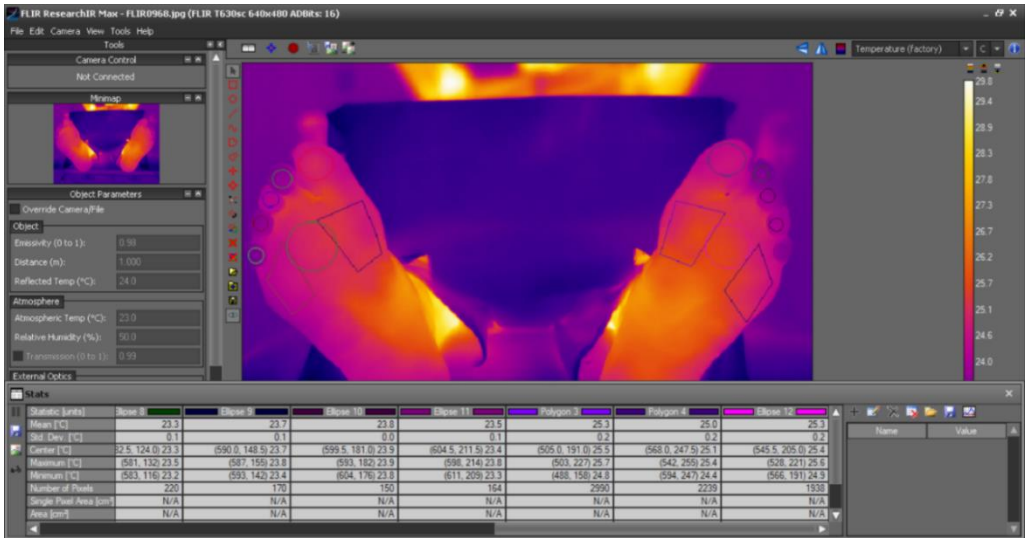

Figure 3.7: Flir Research IR Software

From the temperatures of the thermographic image, the probability of T2DM foot complications was determined.

Probability of T2DM Foot Complications

Detection of T2DM complications using the thermographic camera was done using logistic regression curves and formulas produced from the study by Gatt et al. (2018). Two separate formulas for the toes and forefoot were produced.

For the toes:

$$\log_e\left(\frac{p}{1-p}\right) = -5.786 + 0.220\text{Temp}$$

For the forefoot:

$$\log_e\left(\frac{p}{1-p}\right) = -6.949 + 0.254\text{Temp}$$

In these equations, $\log_e$ refers to the natural logarithm function, i.e. log of *x* base *e*. The 'e', also known as Euler's number, is an irrational constant whose value is approximately equal to 2.71828. The *p* represents the probability that diabetic foot complications are present, *1-p* represents the probability of no complications, and *Temp* represents the cutaneous temperature (^{o}C) of a specific area found on the participant.

To find the probability of complications present, *p* was made the subject of the formula.

For the toes:

$$p = \frac{e^{-5.786+0.220\text{Temp}}}{1+e^{-5.786+0.220\text{Temp}}}$$

For the forefoot:

$$p = \frac{e^{-6.949+0.254\text{Temp}}}{1+e^{-6.949+0.254\text{Temp}}}$$

The cutaneous temperature of every one of the eight regions of interest of every foot was then inserted in the appropriate equation (toes or forefoot), and the probability of complications would be worked out. This was facilitated by using SPSS. Furthermore, for each foot, the average cutaneous temperature of all the toe ROIs and the average cutaneous temperature of all the forefoot ROIs was worked out separately and used in the equations for a more comprehensive and less subjective investigation. Four different probability cut-off points were investigated: 0.4, 0.5, 0.6, and 0.7 probability cut-off points. When the probability was equal to or exceeded the cut-off point being investigated, diabetic foot complications were predicted, and when the probability cut-off point was not exceeded, the foot was predicted to be healthy. Different probability cut-off points were investigated to identify which probability cut-off point that produces the best sensitivity, specificity, NPV and PPV.

Confirmation or Exclusion of T2DM Foot Complications

Medically validated tests consisting of Doppler analysis, tuning fork, and 10g-monofilament sensation testing, were utilized to confirm or rule out T2DM complications of neuropathy and/or PAD. To prevent any potential bias, these tests were conducted by a different podiatrist who was not aware of the outcome of the plantar cutaneous temperature tests.

Doppler Waveform

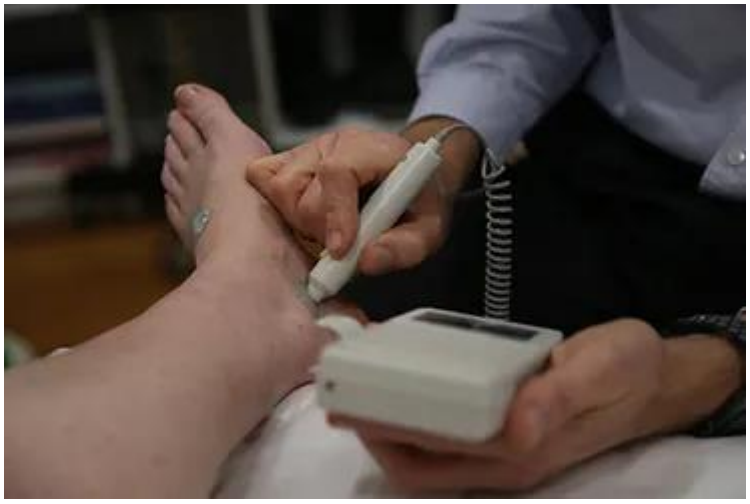

Figure 3.8:Doppler waveform on PT artery

Peripheral circulation was assessed using Doppler waveform analysis. Waveforms were recorded at the Dorsalis Pedis and Posterior tibial arteries using a Hadeco Pocket Doppler ES-100V3 with an 8MHz probe and a screen showing the waveform.

First, the participant`s back was reclined 45º to 60º in Fowler`s position. Ultrasonic gel was first applied on the dorsalis pedis and the posterior tibial arteries. The probe was held at a 45º angle against the arterial blood flow and moved gently to locate the optimal signal. The signal is produced by the wave reflected to the probe by moving erythrocytes (Young et al., 2013).

The type of waveform was then recorded as monophasic, biphasic or triphasic. A triphasic indicates that the artery is healthy and has no signs of PAD. A biphasic indicates some element

of PAD present; however, this is not severe. Monophasic is indicative of PAD (Kim et al., 2020). According to a study conducted by Formosa et al. (2018), experienced clinicians exhibit a high level of interrater reliability when it comes to visual spectral Doppler interpretation.

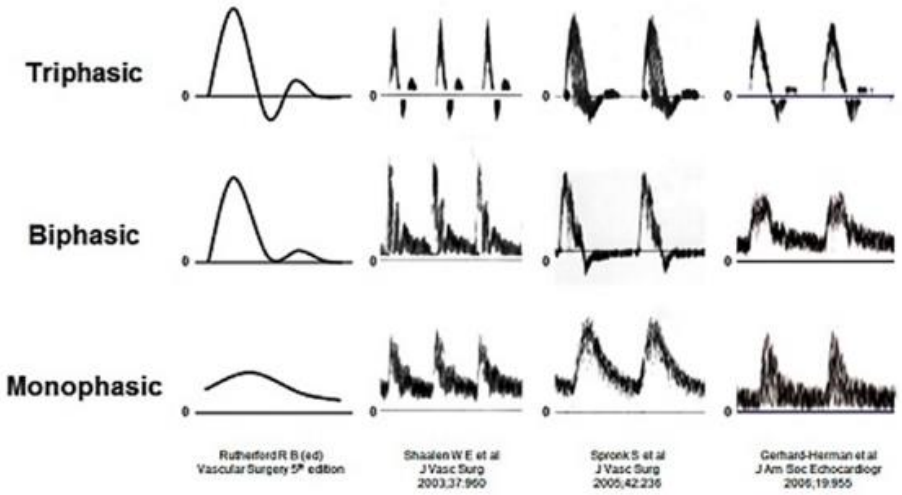

Figure 3.9: Monophasic, biphasic, and triphasic waveforms. Retrieved from Kim et al., 2020.

In a study by Tehan, Bray and Chuter (2016), it was revealed that continuous wave Doppler has the highest sensitivity and specificity in detecting PAD in patients with diabetes and without diabetes when compared to ABPI and TBPI. Alavi et al. (2015) performed a study to determine the accuracy of an audible handheld Doppler ultrasound for the identification of PAD. The study found a sensitivity of 42.8%, a specificity of 97.5%, a negative predictive value of 94.1% and a positive predictive value of 65.2%. Following these results, the authors concluded that the Doppler waveform is a reliable and inexpensive piece of equipment that can exclude PAD in diabetic and non-diabetic patients. Formosa et al. (2018) reported that five skilled podiatric physicians demonstrated a high level of agreement in interpreting spectral Doppler waveforms ($\alpha = 0.98$).

Ankle Brachial Pressure Index

To conduct the ABPI test, we utilised the Dopplex ABPI kit. This comprehensive kit comprises of a DMX digital doppler, a medical-grade recharging kit, a wide beam 8MHz doppler probe, a doppler probe, a sphygmomanometer, and cuffs.

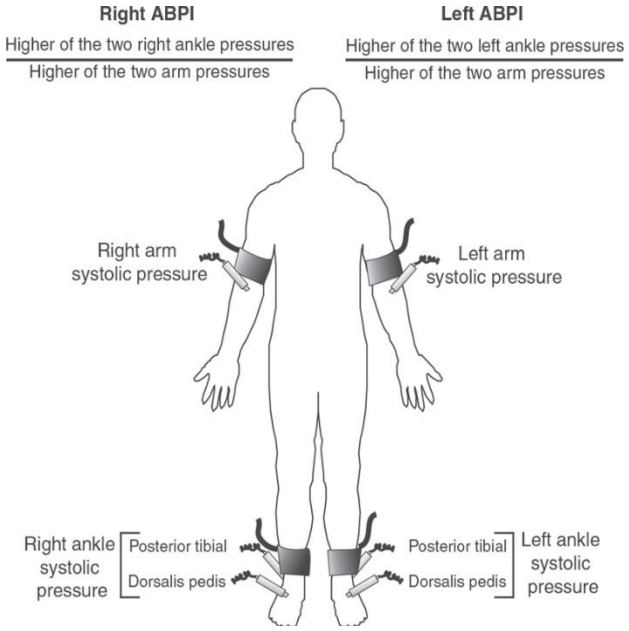

Figure 3.10: ABPI

The ABPI procedure started by reclining the participant in Fowler's position. To measure the systolic pressure of the brachial artery, the cuff was placed above the elbow and ultrasound gel was applied. The Doppler probe was then positioned at a 45^{o} angle against the blood flow. Once the pulse was detected by the Doppler, the cuff was inflated until the pulse could no longer be heard. Afterwards, the cuff was deflated slowly, and the pressure on the sphygmomanometer was noted as soon as the pulse was detected again. The same process was repeated for the other upper limb to determine the highest systolic blood pressure.

Systolic pressure at the ankle was then recorded using the same procedure as above, using the blood pressure of the posterior tibial and anterior tibial arteries. The highest systolic pressure of the ankle (either that of the posterior tibial or anterior tibial artery) is then divided by the

highest systolic pressure of the brachial artery (either left or right upper limb) to produce the ABPI reading.

A systematic search by Brouwers et al. (2022) found that ABPI <0·9 can be useful in diagnosing PAD but failed to rule out PAD. Casey et al. (2019) stated that the inter- and intra-tester reliability of the ABI is acceptable; however, validity was difficult to be determined due to inconsistencies in obtaining systolic pressure measurements, calculating ABI values, and incomplete reporting of methodologies and statistical analysis. Furthermore, a study by Formosa et al. (2013) revealed inconsistencies between ABPI and Doppler waveform results in 35% of 49 participants with T2DM. The authors stated that ABPI and Doppler waveform should be used when screening for PAD in patients with diabetes. In this study, ABPI and Doppler waveform were used to diagnose a participant with PAD. The criteria can be found in Table 3.2.

10 g Semmes Weinstein monofilament

The tuning fork and the 10g-monofilament were used to identify signs of peripheral neuropathy. The monofilament was first applied to the participant`s wrist to get an idea of what to expect. The participants were asked to close their eyes while the monofilament was applied to a few areas around the foot. Sufficient force is applied until the monofilament buckles. The monofilament was applied at random areas around the foot while the participant informed the examiner every time the sensation was felt. The ten tested sites can be seen in Figure 3.11. Peripheral neuropathy was indicated in case of failure to detect at least 1 of the 10 points from monofilament. The 10g monofilament has been found to have a strong diagnostic accuracy in detecting diabetic peripheral neuropathy (Shrestha, Gorkhaly & Bajracharya, 2021).

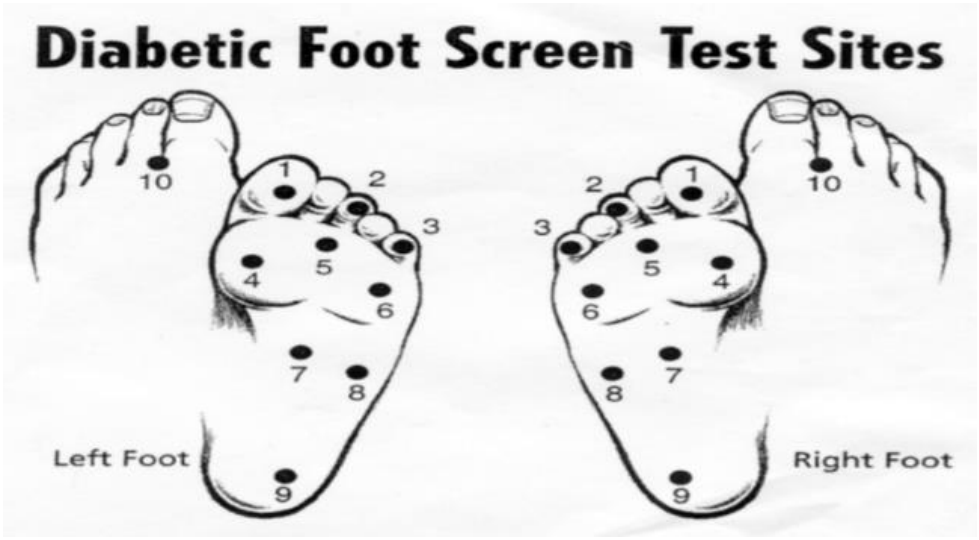

Figure 3.11: Monofilament screening sites

The reliability and validity of Semmes Weinstein monofilament testing in older adults was investigated by Shaffer et al. (2005). Results from their study show that the Semmes Weinstein monofilament testing protocol is a reliable and specific instrument for identifying peripheral sensory neuropathy in older adults.

Feng et al. (2009) stated that in order to exploit the diagnostic value of Semmes Weinstein monofilament testing, a three-site test involving the Hallux, the third MTH, and the fifth MTH should be used. Another study by Shrestha et al. (2021) found very high sensitivity (92%), specificity (95.8%), PPV (88.5%) and NPV (97.1%) when using a monofilament test in identifying loss of protective sensation.

128Hz Tuning Fork

The tuning fork was also used to assess peripheral neuropathy. First, it was activated by striking the tuning fork against the palm of the hand. The tuning fork was then applied to a bony prominence where neuropathy is unlikely such as the elbow or wrist, to allow the subject to become familiar with the vibration sensation. Vibration testing is typically carried out on the ankle and the distal area of the big toe (Azzopardi et al., 2017).

The subject was instructed to indicate when the vibration sensation stopped. When the subject indicated the vibration had stopped, the examiner placed the tuning fork on his wrist. If the examiner still feels vibrations, the subject is considered to have impaired vibration sense (Boulton et al., 2008).

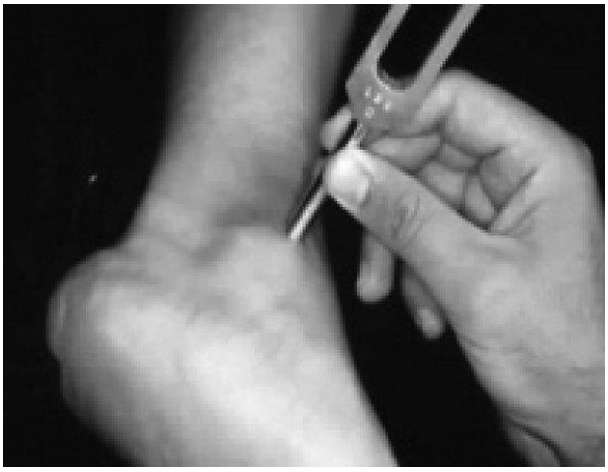

Figure 3.12: 128Hz Tuning fork. Retrieved from Wu et al. (2007)

Meijer et al. (2005) stated that the single use of the 128-Hz tuning fork produces results much better than monofilament regarding validation and predictive value. The authors recommended the use of the tuning fork alone for screening. Cham et al. (2019) performed a study to evaluate the inter-rater and intra-rater reliability of the Semmes Weinstein monofilament and tuning fork to detect pressure and vibration sensations in diabetic patients. Results demonstrate high same-day inter-rater and intra-rater reliability levels for Semmes Weinstein monofilament, 128Hz tuning fork, and 256 Hz tuning fork. Intra-rater reliability when using Semmes Weinstein monofilament remained high when the tests were repeated seven days later; however, that of the tuning fork was found to be moderate. Inter-reliability of Semmes Weinstein monofilament and tuning fork was found to be high and poor respectively when the tests were repeated seven days later. The authors concluded that the Semmes Weinstein monofilament and tuning fork appears to be highly reliable when it comes to assessing pressure and vibration sensations in patients with diabetes.

Comparing Results

To confirm or exclude the presence of T2DM complications, the thermograms of each foot were compared to other medically validated diagnostic tests consisting of ABPI, doppler US, tuning fork, and monofilament. The following criteria based on the study by Gatt et al. (2018) were used to classify the participants as healthy, Ischaemic, Neuropathic, and Neuroischaemic. Feets that did not fall into these categories were excluded from the study. For example, participants with ABPI <0.8 but with biphasic Doppler waveforms were not included.

	Healthy	Ischaemic	Neuropathic	Neuroischaemic
Vascular Assessment	ABPI 0.9-1.3 and triphasic Doppler waveform	ABPI score<0.6 and monophasic Doppler waveforms	ABPI 0.9-1.3 and triphasic Doppler waveform	ABPI score<0.6 and monophasic Doppler waveforms
Neuropathy Assessment	All 10 points from monofilament detected and good vibration perception from tuning fork test	All 10 points from monofilament detected and good vibration perception from tuning fork test	Failure to detect at least 1 of the 10 points from monofilament test and/or reduced vibration perception from tuning fork	Failure to detect at least 1 of the 10 points from monofilament test and/or reduced vibration perception from tuning fork

Table 3:2: Classification of participants into PAD, neuropathy, neuroischaemic or healthy groups.

Statistical Analysis

Statistical analysis is performed after the data is collected; however, earlier planning as part of the research design is important (Myers et al., 2010).

All the necessary data, such as the mean temperatures of all ROIs and results from medically validated tests, were then summarised in an Excel sheet. This data was then transferred to SPSS version 23 so that statistical analysis could be done. The aim of statistical analysis was to determine whether a thermographic camera can be used as a screening modality to detect T2DM complications by extracting the sensitivity, specificity, NPV and PPV.

Earlier in the research, the SPSS was used to work out the probability of T2DM foot complications. As previously stated, if the probability exceeded the cut-off point being investigated, the foot was predicted to have diabetic foot complications and recoded as the number '1' in the SPSS. If the probability was less than the cut-off point being investigated, the foot was predicted as healthy and recoded as the number '2'. The actual presence of foot complications using diagnostic tests was also recoded as the number '1', and actual confirmation of a healthy foot was recoded as '2'. This can be seen in the figure 3.14.

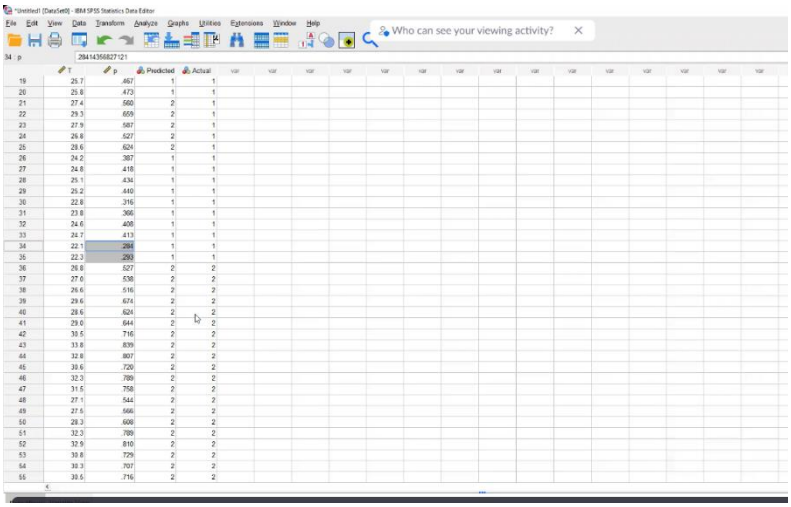

Figure 3.13: Input of data into SPSS

Crosstabulation was used to provide a contingency table showing the relationship between the two variables (actual and predicted). This produced the sensitivity and specificity for each ROI.

Sensitivity and specificity are the statistical measures of the performance of a binary classification test (Habib et al., 2015). Sensitivity measures the true positives among people with the disease, while specificity measures the true negatives among people who do not have the disease. In this study, the sensitivity will measure the number of participants predicted to have T2DM foot complications (using thermography) among the number of participants to actually have T2DM foot complications (diagnosed by medically validated tests).

Predictive Outcome		Actual Outcome		
		Disease Present	Disease Absent	
	Positive Test	True Positive (a)	False Positive (b)	a + b
	Negative Test	False Negative (c)	True Negative (d)	c + d
		a + c	b + d	n

Table 3:3: The concept of sensitivity, specificity, NPV and PPV

Sensitivity is determined by dividing the number of true positives by the total number of actual positives. This can be simplified by the equation below:

$$\text{Sensitivity} = a / (a+c)$$

Specificity is determined by dividing the number of true negatives by the total number of participants that do not have the disease, as seen in the equation below:

$$\text{Specificity} = d / (b+d)$$

The sensitivity and specificity of each ROI were then compared to identify the region and probability cut-off point with the highest sensitivity and specificity.

After the sensitivity and specificity, the positive and negative predictive values were calculated. A major limitation when using sensitivity and specificity alone is that it does not provide the clinician with the probability that the disease is present or absent (Habib et al., 2015). A positive predictive value refers to the proportion of people with a positive test result who actually have the disease. Referring to Table 3.3, this can be calculated as follows:

$$\text{Positive Predictive Value} = a / (a+b)$$

A negative predictive value refers to the proportion of people who tested negative who do not have the disease. Referring to Table 3.3, this can be calculated as follows:

$$\text{Negative Predictive Value} = d / (d+c)$$

Testing for Statistically Significant Differences in Mean Temperatures between Groups.

The Shapiro-Wilk test was used to determine whether the data is normally distributed. When the p-value generated from this test was greater than the 0.5 level of significance, the data was considered to be normally distributed. When the 0.5 level of significance was not exceeded, the distribution of data was considered to be non-normal.

The One-Way ANOVA with post hoc Tukey test was done to determine whether there is a statistically significant difference in mean temperatures between the four groups of T2DM (Healthy, Ischaemic, Neuropathic, and Neuroischaemic) in areas where the data was normally distributed. The Kruskal–Wallis test was used when the data was not normally distributed.

Reliability and Validity of the Study

One of the most important research issues is ensuring reliability and validity. Reliability refers to the consistency of a measure (Price et al., 2015). Reliability can be described as a measurement that examines the consistency, precision, repeatability, and trustworthiness of research (Chakrabartty, 2013). According to Joppe (2000), a study can be considered as reliable if there is an accurate representation of the total population and the study can be reproduced under a similar methodology. Therefore, to ensure the reliability of a research study, a detailed

description of the procedure is of utmost importance (Kirk & Miller, 1986). To ensure reliability, this research includes detailed research methods and research design, sample setting procedure, and detailed statistical analysis.

There are three categories of reliability. The first is test-retest reliability, which refers to the repeatability of results when the same study is repeated on the same population. The second is internal consistency, which measures the correlation between multiple variables in a test designed to measure the same construct. Finally, interrater reliability refers to the consistency of results produced by different researchers when the study is repeated under the same conditions. (Price et al., 2015).

In quantitative research, to assurance that the results of a study accurately reflect the truth in the population being investigated and not the result of any errors in the methodology (Patino and Ferreira, 2018). The three types of validity in quantitative research are external validity, internal validity, and content/construct validity.

Internal validity indicates whether the results of the research are legitimate by the way of how a study is designed and conducted. Internally valid research needs to be done to eliminate bias and allow for accurate conclusions about the relationship between the independent and dependent variables (Tashakkori and Teddlie, 2010). A study has high internal validity if it is well-designed, well-executed, and the results accurately reflect the causal relationship between the variables under investigation. In this study high level of internal validity is indicated if the results obtained from the sample population of people with T2DM foot complications accurately reflect the outcomes that would be found in the entire population of T2DM patients with foot complications.

External validity, on the other hand, refers to the generalizability of a study's findings to other groups of interest (Dellinger and Leech, 2007). External validity can be increased by sampling techniques, usage of heterogeneous groups, usage of non-reactive measures, and detailed description that allows replication of the research across different populations (Rothwell, 2006). Several factors can influence external validity. The highly selective inclusion/exclusion criteria in this research would pose a threat to external validity as these criteria cannot be easily reproduced in the clinical setting (Rothwell, 2006). Inconsistencies when following procedures throughout the entire research can also decrease external validity. Detailed research methods and methodology made sure that this was not the case regarding this research.

Content validity refers to the extent to which a study's instruments or procedures adequately measure what these are intended to measure. An example in this research is the Doppler waveform and ABPI measuring the extent of PAD. Threat to content validity happens when researchers use poor definitions and calculate variables based on those poor definitions (Modell, 2005).

Conclusion

In this chapter, a comprehensive framework for this research was presented. This included the philosophical stance, research approach, and research method utilized to achieve the research's objectives. Through the application of this methodology, the research was successful in identifying the sensitivity, specificity, positive predictive value, and negative predictive value of thermography at varying probability cut-off points. The upcoming chapter will feature a detailed account of all the results obtained in this research, which will be further analyzed and discussed in Chapter 5.

Chapter 4 : Results

Descriptive Statistics

This research included 64 feet from 32 participants. Of the 32 participants, eighteen were male (56.25 %) and fourteen were female (43.75%). The age range varied from 47 to 89, averaging 74 (range = 42 years; standard deviation=12.44).

Each foot was recorded and analysed separately. This was done because the presence and severity of diabetic foot disease vary from one foot to another of the same individual (Holowka & Lieberman, 2018). Only one participant had 2nd digit amputation due to trauma during the teenage years. No participants with active ulcers at the time of the study were recruited. None of the participants had a history of angioplasty or lower extremity bypass surgery.

Mean Temperatures for every ROI

The following table represents the mean, standard deviation, range, and minimum and maximum temperatures recorded for each ROI.

	N	Minimum (^{o}C)	Maximum (^{o}C)	Mean (^{o}C)	Std. Deviation
Hallux	64	21.80	33.80	27.3383	3.16147
2nd Toe	63	21.80	33.40	26.9571	3.13902
3rd Toe	64	21.90	33.60	27.0266	3.12010
4th Toe	64	22.10	33.70	27.0664	3.06003
5th Toe	64	22.10	33.50	27.1117	3.09083
Toes Average	64	22.00	33.60	27.1041	3.07945
1st MTH	64	23.50	33.70	28.6031	2.62727
3rd MTH	64	23.70	33.70	28.5859	2.66547
5th MTH	64	23.70	32.60	28.2250	2.64545
F/F Average	64	23.63	33.27	28.4717	2.63273

Table 4:1: Minimum, Maximum, Mean & Standard Deviation of Plantar Foot Temperatures of Recruited Participants

Study population

Following a series of medically validated tests, including ABPI, doppler US, 10g monofilament, and 128Hz tuning fork, it was determined that 35 feet were in good health, while 12 feet exhibited signs of ischemia, 9 feet showed indications of neuropathy, and 8 feet displayed a combination of both neuropathy and ischemia.

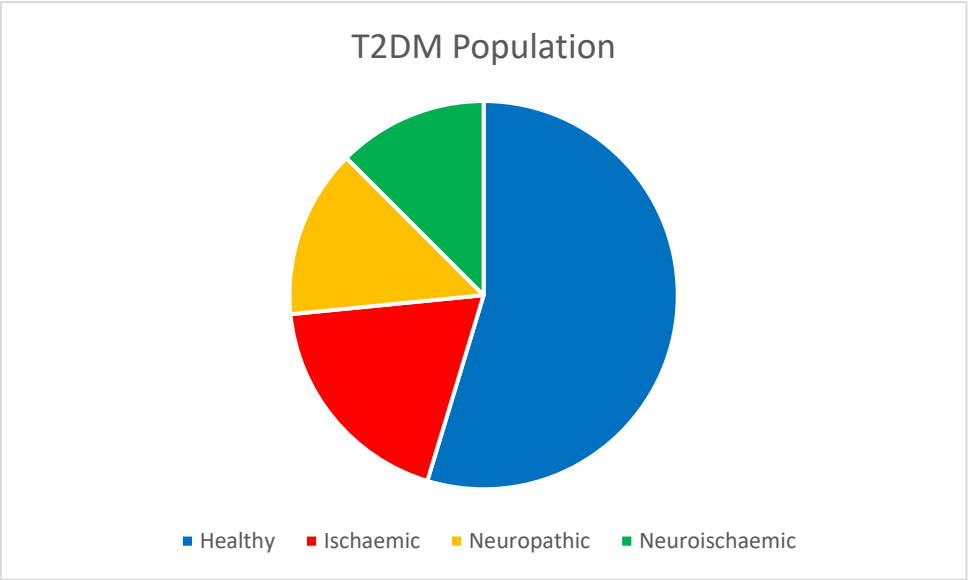

Figure 4.1: Study Population

Toe Temperatures

The first statistical test was to analyse the toe temperatures. The toe temperatures for each participant were input inside the equation provided by Gatt et al. (2018). Temp refers to the recorded temperature of the ROI, and *p* refers to the probability of complications. To determine the probability of the presence of T2DM foot complications, *p* was made the subject of the formula.

$$\log_e\left(\frac{p}{1-p}\right) = -5.786 + 0.220\text{Temp}$$

$$\frac{p}{1-p} = e^{-5.786+0.220\text{Temp}}$$

$$p = \frac{e^{-5.786+0.220\text{Temp}}}{1+e^{-5.786+0.220\text{Temp}}}$$

This equation was used for all the ROIs in the toes. Since forefoot temperatures differ from the toes, another equation was used for the forefoot ROIs.

Analysis of Average Toes Temperatures

Based on the mean temperature of the ROI being investigated, the probability of T2DM complications for each foot was provided separately. For the purpose of this research, four different probability cut-off points were investigated in order to decide which cut-off point represented the optimal point at which a decision could be made. These were 0.4, 0.5, 0.6, and 0.7. Sensitivity and specificity for every ROI and probability cut-off point were recorded. If the probability of complications exceeded the probability cut-off point being investigated, T2DM foot complications were hypothesized as being present. As pointed out in the methodology chapter, medically validated tests consisting of Doppler, ABPI, 10g monofilament, and 128Hz tuning fork were conducted by another podiatrist in order to categorise each limb as either healthy, ischaemic, neuropathic or neuroischaemic, thus confirming or excluding the presence of T2DM complications.

Sensitivity, Specificity, NPV and PPV for Average Toes ROI

- The predicted outcome was compared to the actual outcome to determine each ROI's sensitivity, specificity, NPV and PPV.
- Those participants correctly predicted to have T2DM complications were divided by the number of participants that actually have T2DM complications to determine the sensitivity.
- Participants correctly predicted to be healthy were divided by the total number of participants who were actually healthy to determine the specificity (Stojanovic et al., 2014).

- The number of true positives was divided by the total number of participants predicted to have foot complications to determine the PPV.
- The number of true negatives was divided by the total number of participants predicted to be healthy to determine the NPV. These terms are explained in detail at the end of Chapter 3.

Average Toes (0.4 cut-off point)		Actual Outcome		
		No Complications Present	Complications Present	Total
Predicted Outcome	Less Likely to Have Complications	13	0	13
	More Likely to Have Complications	22	29	51
Total		35	29	64

Table 4:2: Actual vs Predicted Outcome of Average Toes ROI (0.4 Probability Cut-off Point)

Specificity	13/35=0.37	Sensitivity	29/29=1
NPV	13/13 = 1	PPV	29/51= 0.58

Table 4:3: Results of Average Toes ROI (0.4 Probability Cut-off Point)

Average Toes (0.5 cut-off point)		Actual Outcome		
		No Complications Present	Complications Present	Total
Predicted Outcome	Less Likely to Have Complications	26	2	28
	More Likely to Have Complications	9	27	36
Total		35	29	64

Table 4:4: Actual vs Predicted Outcome of Average Toes ROI (0.5 Probability Cut-off Point)

Specificity	26/35=0.74	Sensitivity	27/29=0.93
NPV	26/28=0.93	PPV	27/36=0.75

Table 4:5: Results of Average Toes ROI (0.5 Probability Cut-off Point)

Average Toes (0.6 cut-off point)		Actual Outcome		
		No Complications Present	Complications Present	Total
Predicted Outcome	Less Likely to Have Complications	33	9	42
	More Likely to Have Complications	2	20	22
Total		35	29	64

Table 4:6: Actual vs Predicted Outcome of Average Toes ROI (0.6 Probability Cut-off Point)

Specificity	33/35=0.94	Sensitivity	20/29=0.69
NPV	33/42=0.79	PPV	20/22=0.91

Table 4:7: Results of Average Toes ROI (0.6 Probability Cut-off Point)

Average Toes (0.7 cut-off point)		Actual Outcome		
		No Complications Present	Complications Present	Total
Predicted Outcome	Less Likely to Have Complications	35	18	53
	More Likely to Have Complications	0	11	11
Total		35	29	

Table 4:8: Actual vs Predicted Outcome of Average Toes ROI (0.7 Probability Cut-off Point)

Specificity	35/35=1	Sensitivity	11/29=0.38
NPV	35/53=0.66	PPV	11/11=1

Table 4:9: Results of Average Toes ROI (0.7 Probability Cut-off Point)

A graph showing the probability of complications against temperature was created for every ROI. This demonstrates the increase in the probability of complications with an increase in plantar cutaneous temperature.

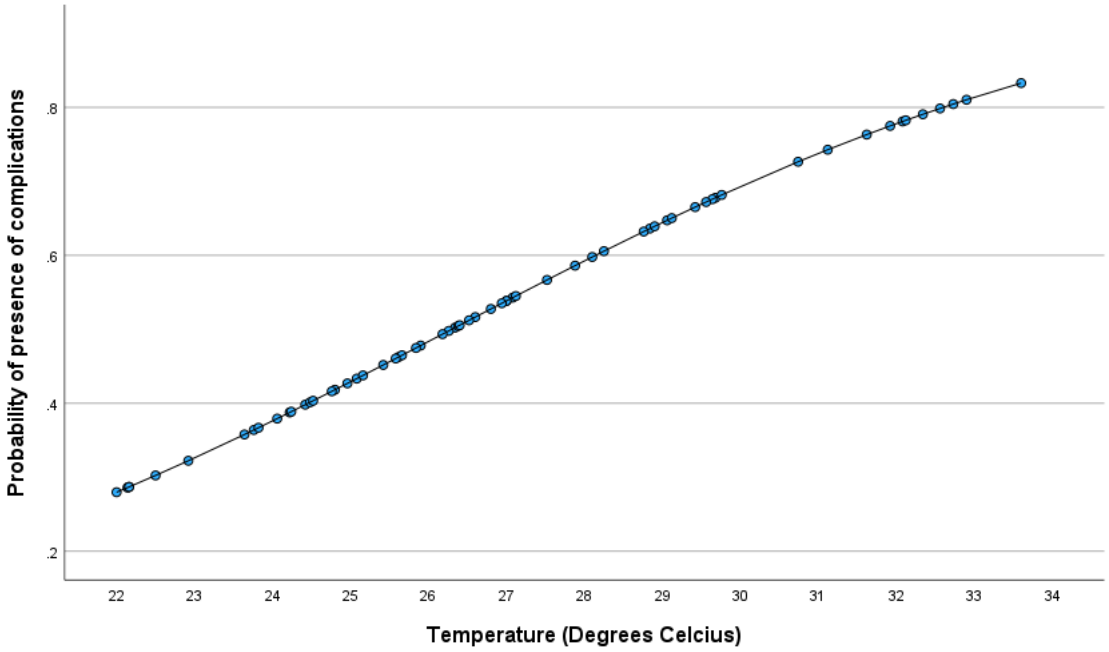

Figure 4.2: Probability of Complications against Temperature Graph (Average Toes)

A graph was also created demonstrating how the sensitivity and specificity change with different probability cut-off points for every ROI. This graph shows that sensitivity decreases, and specificity increases with an increase in the probability cut-off point.

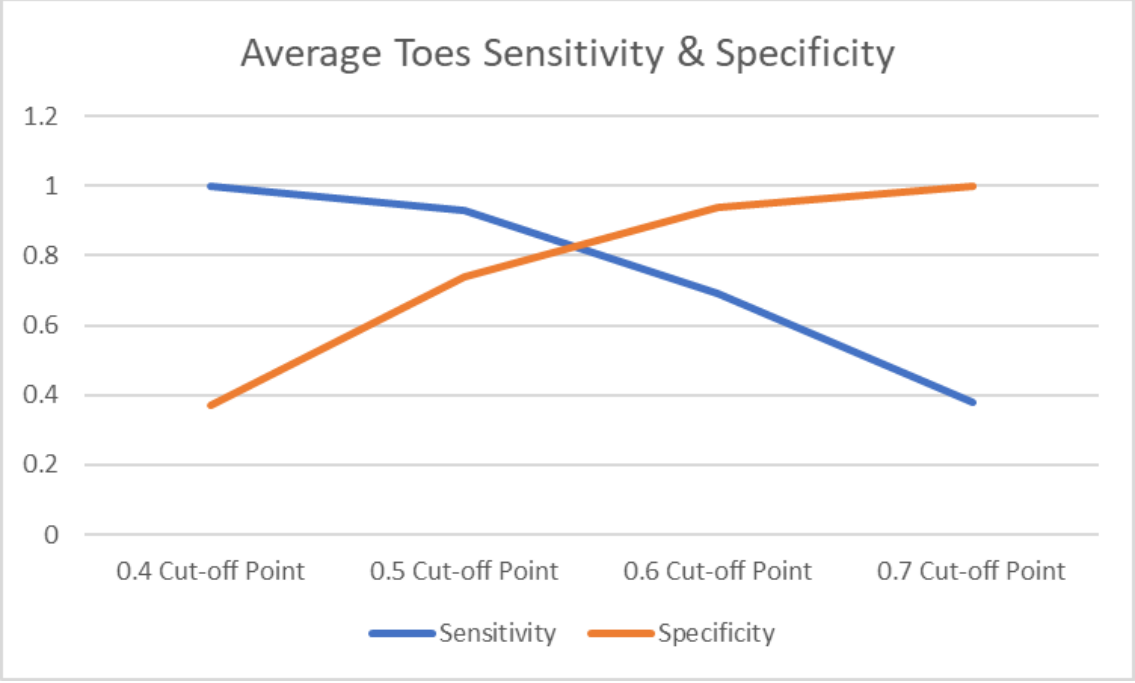

Figure 4.3: Sensitivity & Specificity vs. Probability Graph (Average Toes)

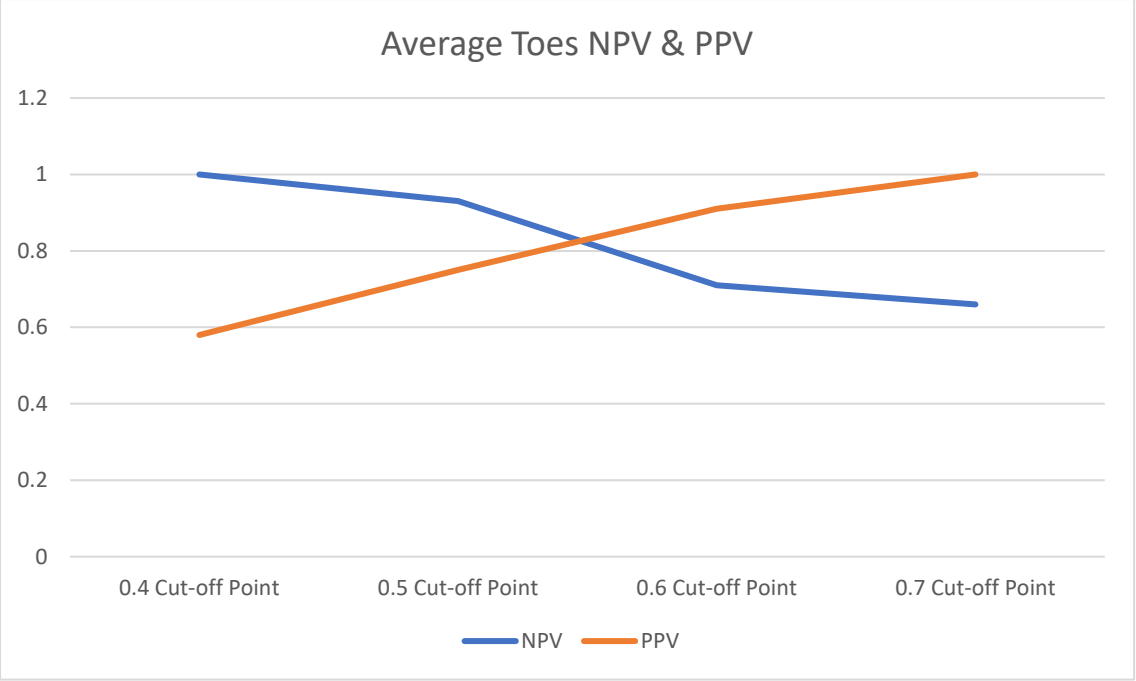

Figure 4.4: Negative Predictive Value vs Positive Predictive Value Graph (Average Toes)

The NPV and PPV are measures to determine what percentage of negative and positive tests were correctly predicted. This graph demonstrates that with an increase in probability cut-off point, there is an increase in the percentage of participants who were predicted to have T2DM foot complications by thermography, that were later confirmed to have T2DM foot complications via medically validated tests. With a decrease in probability cut-off point, there was an increase in the percentage of participants predicted to have healthy feet that were later found to be healthy using medically validated tests.

These steps were repeated to determine sensitivity and specificity for every ROI and can be found in the following sections within this chapter. A summary of the sensitivity and specificity for every ROI in the toes and forefoot can be found in Table 4.50 to Table 4.55 and Table 4.88 to Table 4.91.

Analysis of Hallux Temperatures

Hallux (0.4 Cut-off point)		Actual Outcome		
		No Complications Present	Complications Present	Total
Predicted Outcome	Less Likely to Have Complications	11	0	11
	More Likely to Have Complications	24	29	53
Total		35	29	

Table 4:10: Actual vs. Predicted Outcome of Hallux ROI (0.4 Probability Cut-off Point)

Specificity	11/35=0.31	Sensitivity	29/29=1
NPV	11/11=1	PPV	29/53=0.55

Table 4:11: Results of Hallux ROI (0.4 Probability Cut-off Point)

Hallux (0.5 Cut-off point)		Actual Outcome		
		No Complications	Complications Present	Total
Predicted Outcome	Less Likely to Have Complications	24	2	26
	More Likely to Have Complications	11	27	38
Total		35	29	

Table 4:12: Actual vs. Predicted Outcome of Hallux ROI (0.5 Probability Cut-off Point)

Specificity	24/35=0.69	Sensitivity	27/29=0.93
NPV	24/26=0.92	PPV	27/38=0.71

Table 4:13: Results of Hallux ROI (0.5 Probability Cut-off Point)

Hallux (0.6 Cut-off point)		Actual Outcome		
		No Complications Present	Complications Present	Total
Predicted Outcome	Less Likely to Have Complications	32	8	40
	More Likely to Have Complications	3	21	24
Total		35	29	

Table 4:14: Actual vs. Predicted Outcome of Hallux ROI (0.6 Probability Cut-off Point)

Specificity	32/35=0.91	Sensitivity	21/29=0.72
NPV	32/40=0.8	PPV	21/24=0.88

Table 4:15: Results of Hallux ROI (0.6 Probability Cut-off Point)

Hallux (0.7 Cut-off point)		Actual Outcome		
		No Complications	Complications Present	Total
Predicted Outcome	Less Likely to Have Complications	35	16	51
	More Likely to Have Complications	0	13	13
Total		35	29	

Table 4:16: Actual vs. Predicted Outcome of Hallux ROI (0.7 Probability Cut-off Point)

Specificity	35/35=1	Sensitivity	13/29=0.45
NPV	35/51=0.69	PPV	13/13=1

Table 4:17: Results of Hallux ROI (0.7 Probability Cut-off Point)

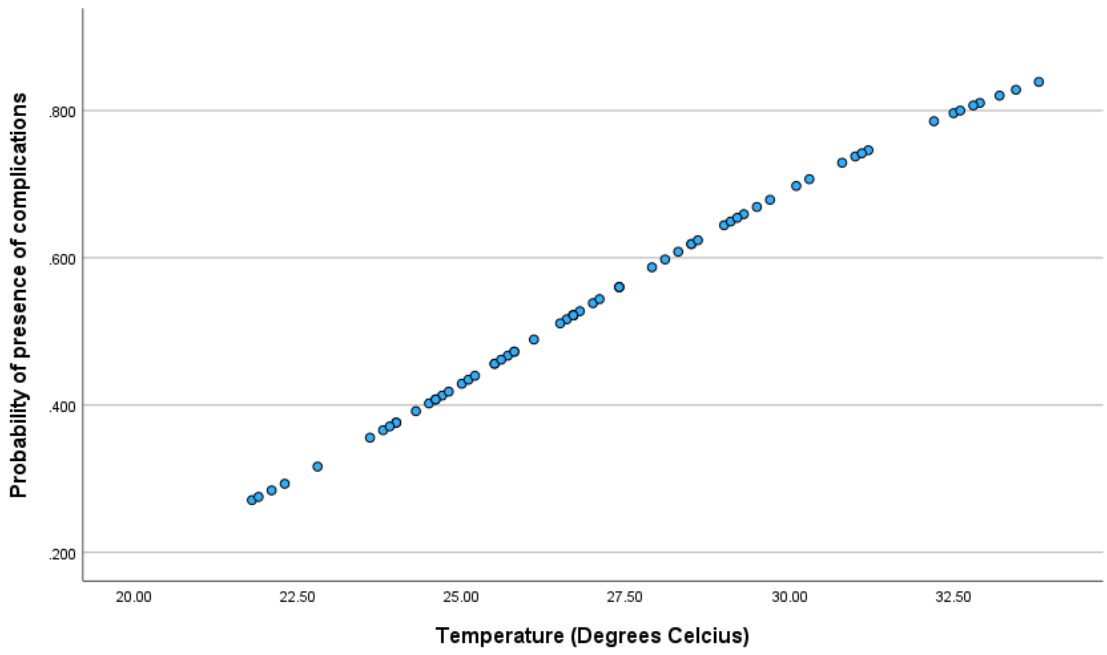

Figure 4.5: Probability of Complications against Temperature Graph (Hallux)

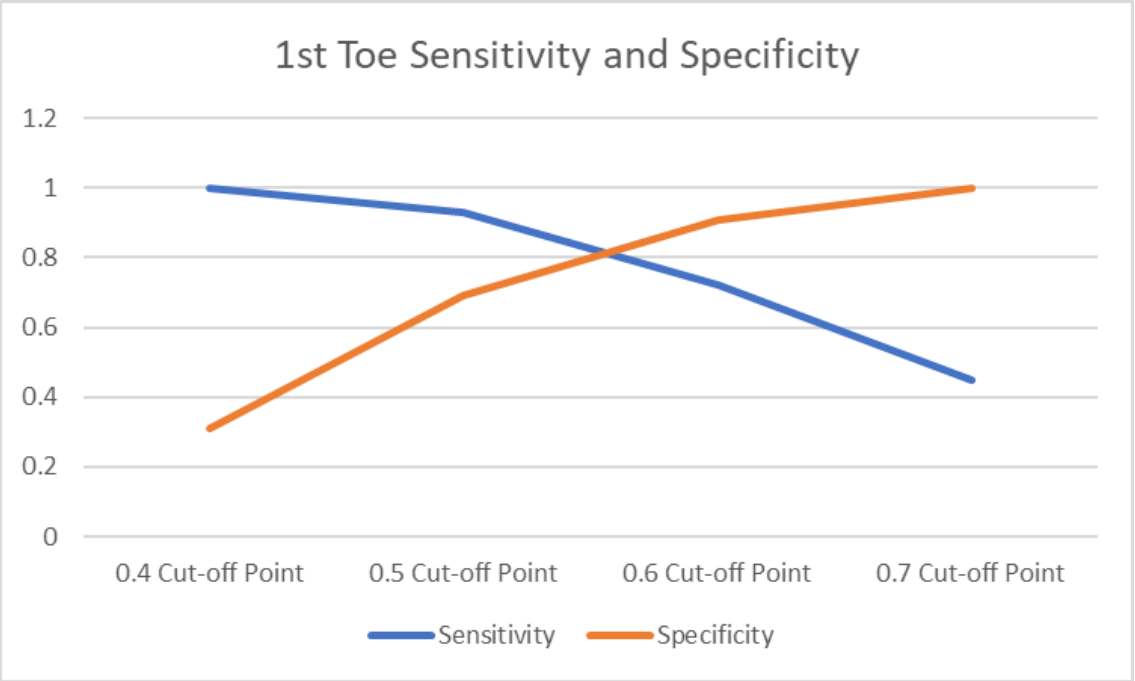

Figure 4.6: Sensitivity & Specificity vs. Probability Graph (Hallux)

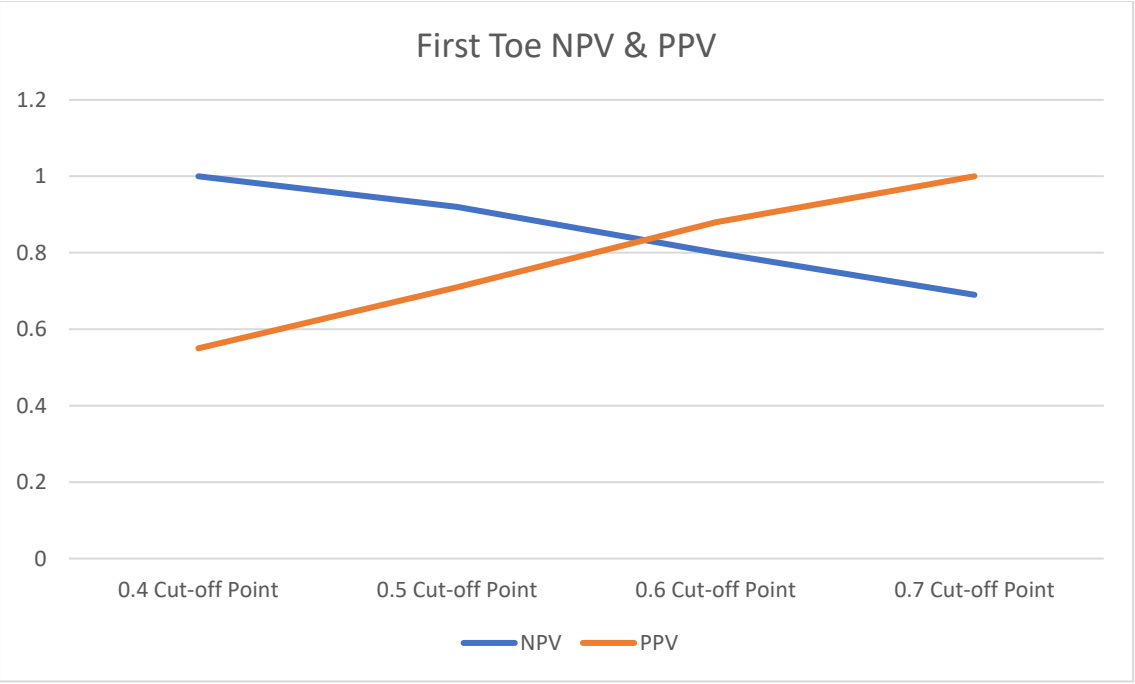

Figure 4.7: Negative Predictive Value vs. Positive Predictive Value Graph (Hallux)

Analysis of 2nd Toe Temperatures

2nd Toe (0.4 cut-off point)		Actual Outcome		
		No Complications Present	Complications Present	Total
Predicted Outcome	Less Likely to Have Complications	15	0	15
	More Likely to Have Complications	20	28	48
Total		35	28	63

Table 4:18: Actual vs. Predicted Outcome of 2nd Toe ROI (0.4 Probability Cut-off Point)

Specificity	15/35=0.43	Sensitivity	28/28=1
NPV	15/15=1	PPV	28/48=0.58

Table 4:19: Results of 2nd Toe ROI (0.4 Probability Cut-off Point)

2nd Toe (0.5 cut-off point)		Actual Outcome		
		No Complications Present	Complications Present	Total
Predicted Outcome	Less Likely to Have Complications	27	2	29
	More Likely to Have Complications	8	26	34
Total		35	28	63

Table 4:20: Actual vs. Predicted Outcome of 2nd Toe ROI (0.5 Probability Cut-off Point)

Specificity	27/35=0.77	Sensitivity	26/28=0.93
NPV	27/29=0.93	PPV	26/34=0.76

Table 4:21: Results of 2nd Toe ROI (0.5 Probability Cut-off Point)

2nd Toe (0.6 cut-off point)		Actual Outcome		
		No Complications Present	Complications Present	Total
Predicted Outcome	Less Likely to Have Complications	32	10	42
	More Likely to Have Complications	3	18	21
Total		35	28	63

Table 4:22: Actual vs Predicted Outcome of 2nd Toe ROI (0.6 Probability Cut-off Point)

Specificity	32/35=0.91	Sensitivity	18/28=0.64
NPV	32/42=0.76	PPV	18/21=0.86

Table 4:23: Results of 2nd Toe ROI (0.6 Probability Cut-off Point)

2nd Toe (0.7 cut-off point)		Actual Outcome		
		No Complications	Complications Present	Total
Predicted Outcome	Less Likely to Have Complications	35	16	51
	More Likely to Have Complications	0	12	12
Total		35	28	63

Table 4:24: Actual vs. Predicted Outcome of 2nd Toe ROI (0.7 Probability Cut-off Point)

Specificity	35/35=1	Sensitivity	12/28=0.43
NPV	35/51=0.67	PPV	12/12=1

Table 4:25:Results of 2nd Toe ROI (0.7 Probability Cut-off Point)

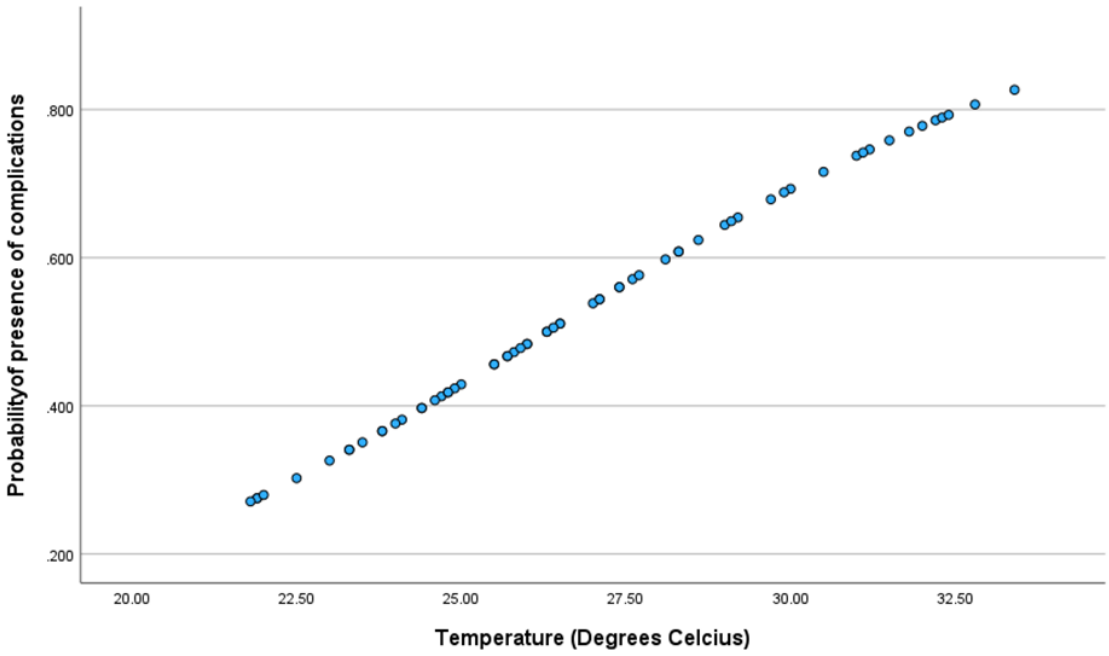

Figure 4.8: Probability of Complications against Temperature Graph (2nd Toe)

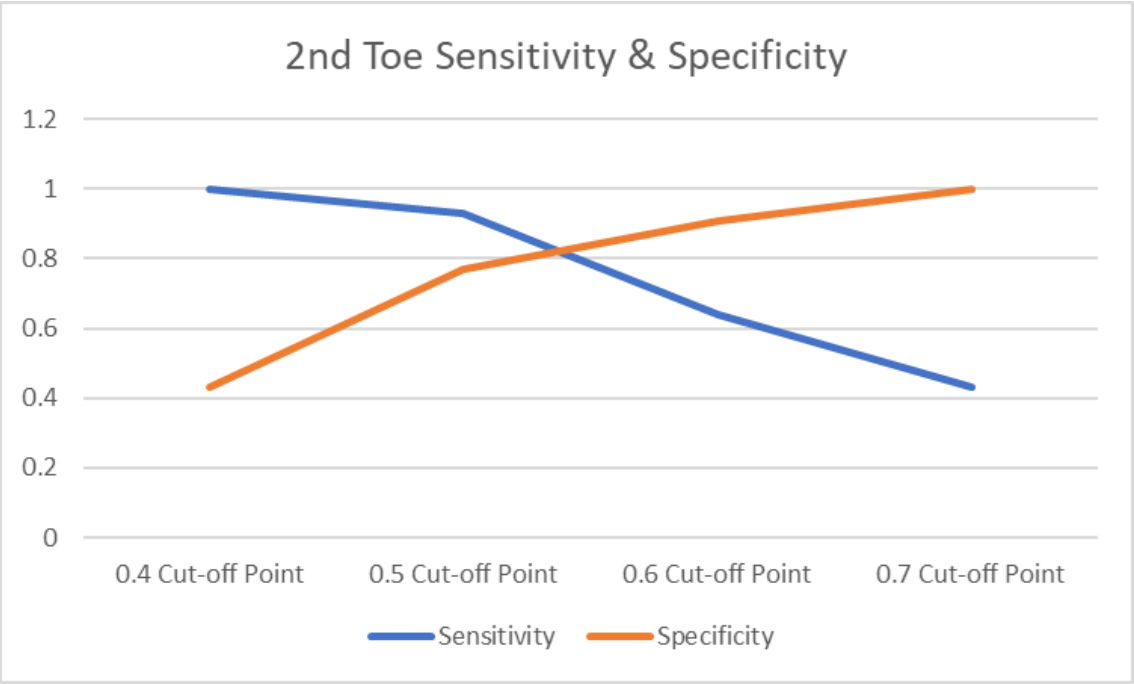

Figure 4.9: Sensitivity & Specificity vs. Probability Graph (2nd Toe)

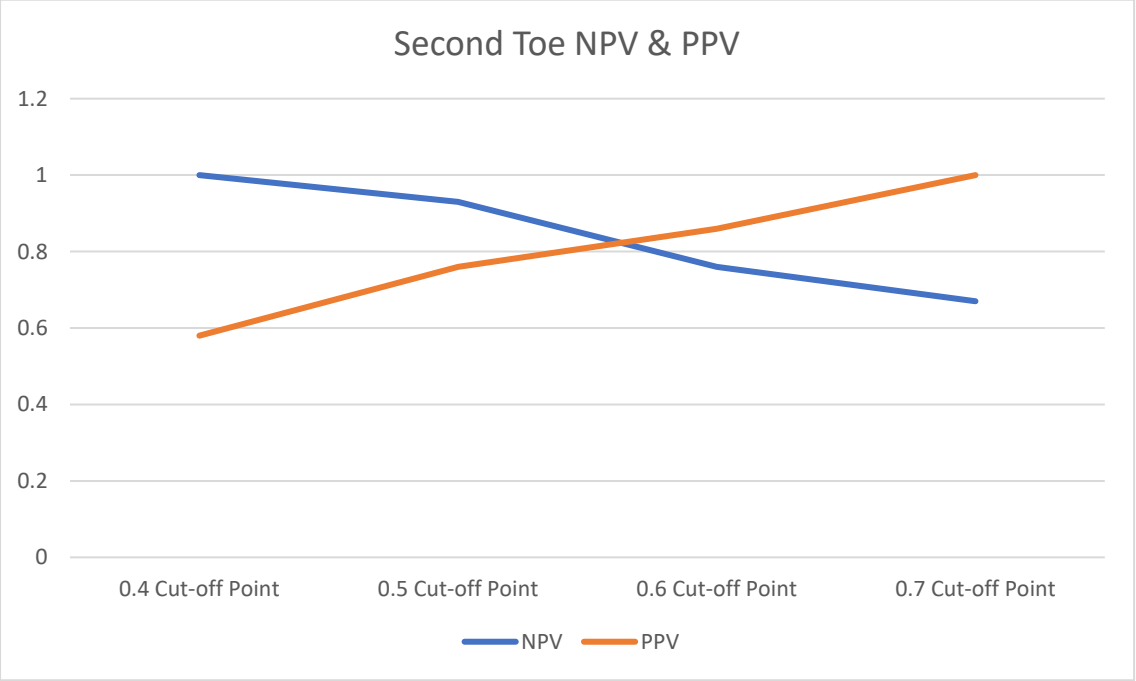

Figure 4.10: Negative Predictive Value vs. Positive Predictive Value Graph (2nd Digit)

Analysis of 3rd Toe Temperatures

3rd Toe (0.4 cut-off point)		Actual Outcome		
		No Complications Present	Complications Present	Total
Predicted Outcome	Less Likely to Have Complications	14	0	14
	More Likely to Have Complications	21	29	50
Total		35	29	64

Table 4:26: Actual vs. Predicted Outcome of 3rd Toe ROI (0.4 Probability Cut-off Point)

Specificity	14/35=0.4	Sensitivity	29/29=1
NPV	14/14=1	PPV	29/50=0.58

Table 4:27: Results of 3rd Toe ROI (0.4 Probability Cut-off Point)

3rd Toe (0.5 cut-off point)		Actual Outcome		
		No Complications Present	Complications Present	Total
Predicted Outcome	Less Likely to Have Complications	27	2	29
	More Likely to Have Complications	8	27	35
Total		35	29	64

Table 4:28: Actual vs. Predicted Outcome of 3rd Toe ROI (0.5 Probability Cut-off Point)

Specificity	27/35=0.77	Sensitivity	27/29=0.93
NPV	27/29=0.93	PPV	27/35=0.77

Table 4:29: Results of 3rd Toe ROI (0.5 Probability Cut-off Point)

3rd Toe (0.6 cut-off point)		Actual Outcome		
		No Complications Present	Complications Present	Total
Predicted Outcome	Less Likely to Have Complications	31	10	41
	More Likely to Have Complications	4	19	23
Total		35	29	64

Table 4:30: Actual vs. Predicted Outcome of 3rd Toe ROI (0.6 Probability Cut-off Point)

Specificity	31/35=0.89	Sensitivity	19/29=0.66
NPV	31/41=0.76	PPV	19/23=0.83

Table 4:31: Results of 3rd Toe ROI (0.6 Probability Cut-off Point)

3rd Toe (0.7 cut-off point)		Actual Outcome		
		No Complications Present	Complications Present	Total
Predicted Outcome	Less Likely to Have Complications	35	17	52
	More Likely to Have Complications	0	12	12
Total		35	29	64

Table 4:32: Actual vs. Predicted Outcome of 3rd Toe ROI (0.7 Probability Cut-off Point)

Specificity	35/35=1	Sensitivity	12/29=0.41
NPV	35/52=0.67	PPV	12/12=1

Table 4:33: Results of 3rd Toe ROI (0.7 Probability Cut-off Point)

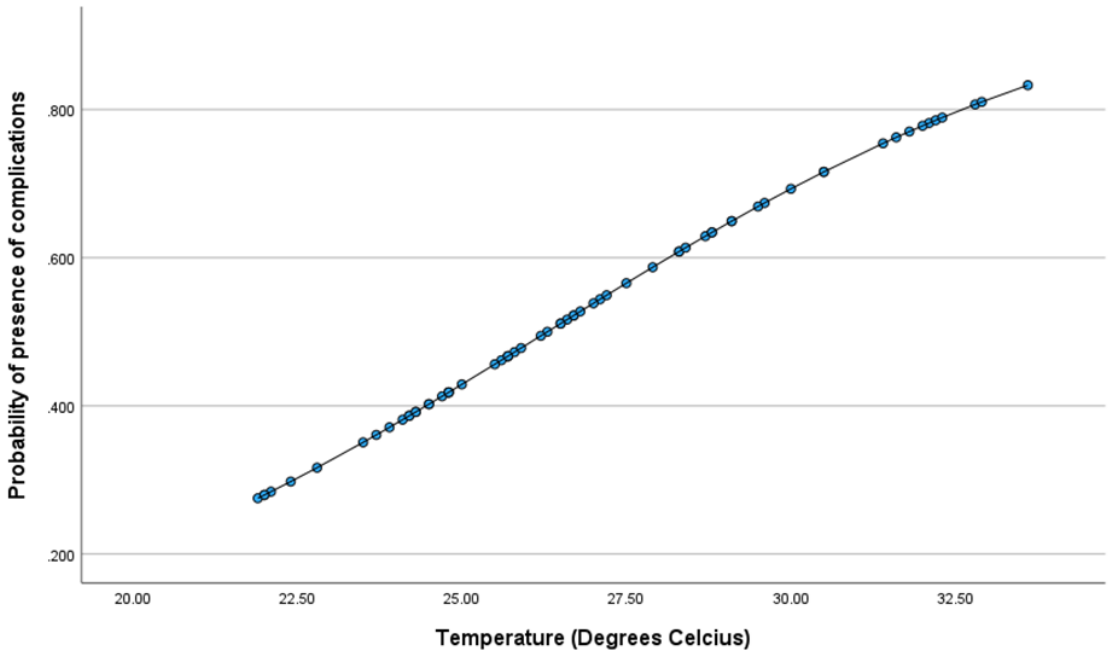

Figure 4.11: Probability of Complications against Temperature Graph (3rd Toe)

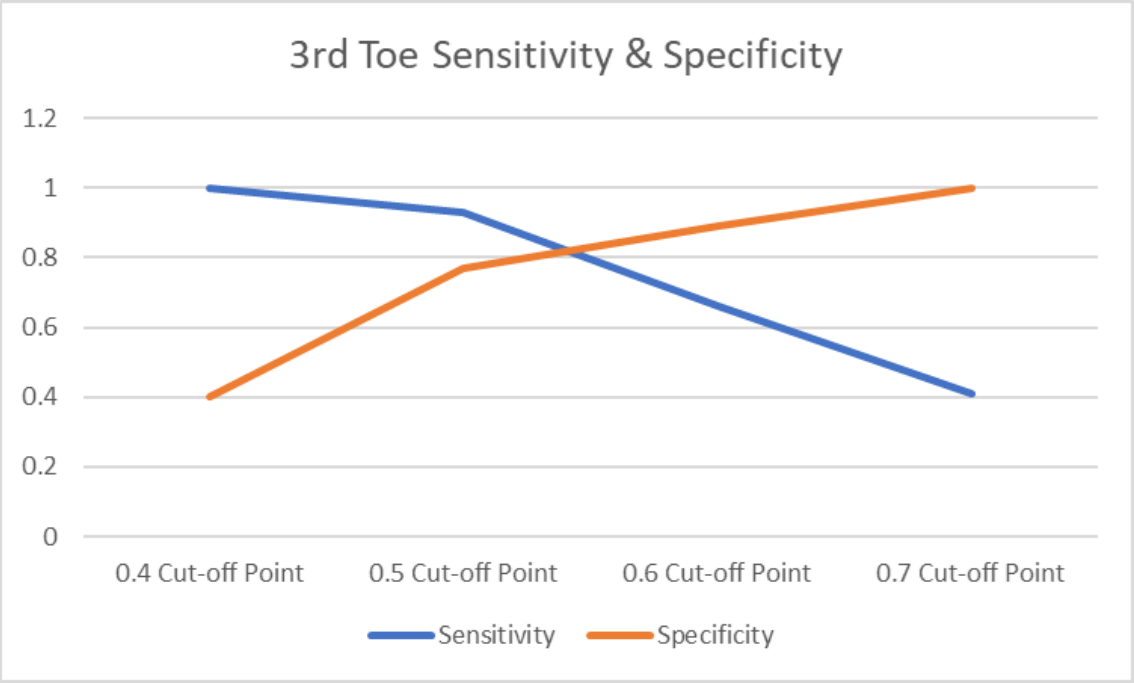

Figure 4.12: Sensitivity & Specificity vs. Probability Graph (3rd Toe)

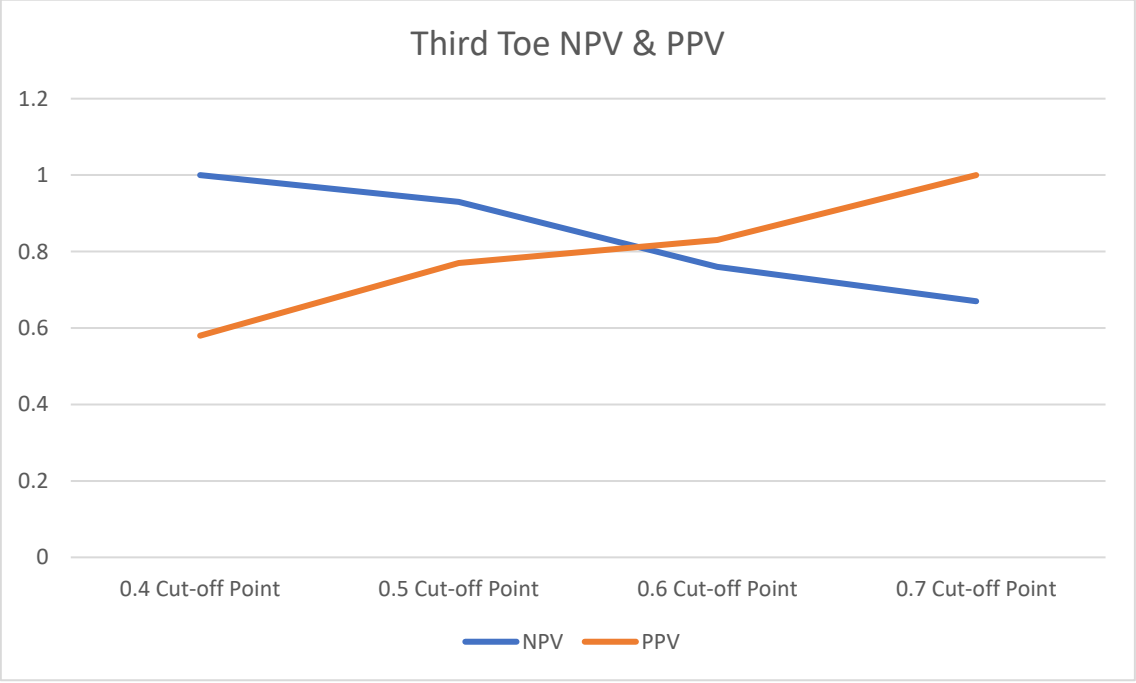

Figure 4.13: Negative Predictive Value vs. Positive Predictive Value Graph (3rd Digit)

Analysis of 4th Toe Temperatures

4th Toe (0.4 cut-off point)		Actual Outcome		
		No Complications Present	Complications Present	Total
Predicted Outcome	Less Likely to Have Complications	11	0	11
	More Likely to Have Complications	24	29	53
Total		35	29	64

Table 4:34: Actual vs. Predicted Outcome of 4th Toe ROI (0.4 Probability Cut-off Point)

Specificity	11/35=0.31	Sensitivity	29/29=1
NPV	11/11=1	PPV	29/53=0.55

Table 4:35: Results of 4th Toe ROI (0.4 Probability Cut-off Point)

4th Toe (0.5 cut-off point)		Actual Outcome		
		No Complications Present	Complications Present	Total
Predicted Outcome	Less Likely to Have Complications	26	1	27
	More Likely to Have Complications	9	28	37
Total		35	29	64

Table 4:36: Actual vs. Predicted Outcome of 4th Toe ROI (0.5 Probability Cut-off Point)

Specificity	26/35=0.74	Sensitivity	28/29=0.97
NPV	26/27=0.96	PPV	28/37=0.76

Table 4:37: Results of 4th Toe ROI (0.5 Probability Cut-off Point)

4^{th} Toe (0.6 cut-off point)		Actual Outcome		
		No Complications Present	Complications Present	Total
Predicted Outcome	Less Likely to Have Complications	33	10	43
	More Likely to Have Complications	2	19	21
Total		35	29	64

Table 4:38: Actual vs. Predicted Outcome of 4th Toe ROI (0.6 Probability Cut-off Point)

Specificity	33/35=0.94	Sensitivity	19/29=0.66
NPV	33/43=0.77	PPV	19/21=0.9

Table 4:39: Results of 4th Toe ROI (0.6 Probability Cut-off Point)

4th Toe (0.7 cut-off point)		Actual Outcome		
		No Complications Present	Complications Present	Total
Predicted Outcome	Less Likely to Have Complications	35	16	51
	More Likely to Have Complications	0	13	13
Total		35	29	64

Table 4:40: Actual vs. Predicted Outcome of 4th Toe ROI (0.7 Probability Cut-off Point)

Specificity	35/35=1	Sensitivity	13/29=0.45
NPV	35/51=0.69	PPV	13/13=1

Table 4:41: Results of 4th Toe ROI (0.7 Probability Cut-off Point)

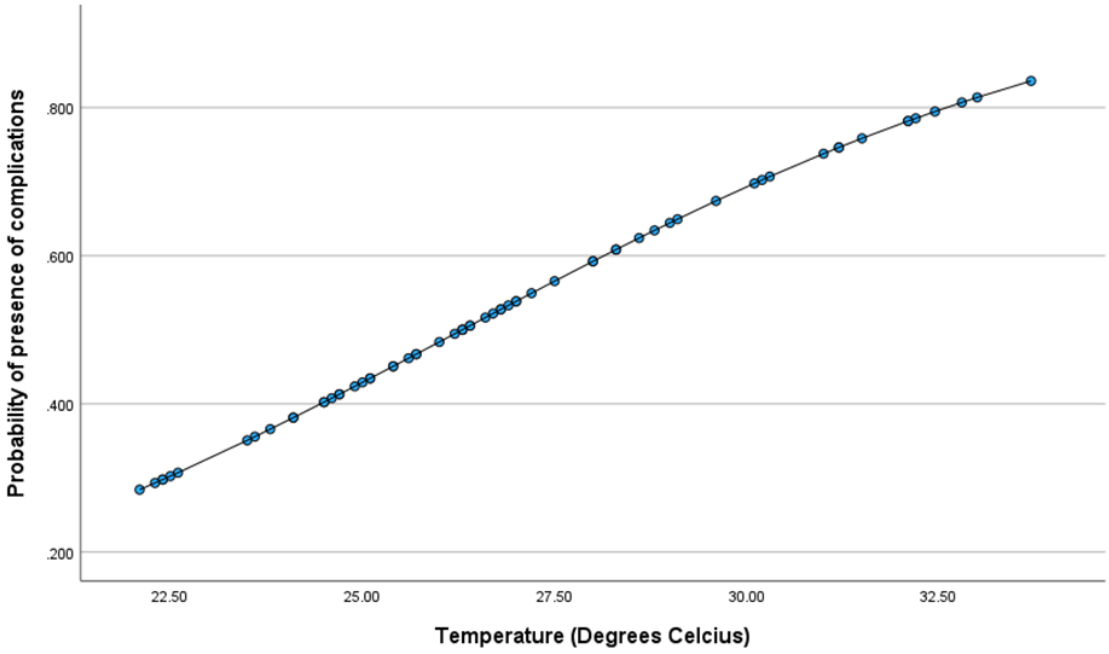

Figure 4.14: Probability of Complications against Temperature Graph (4th Toe)

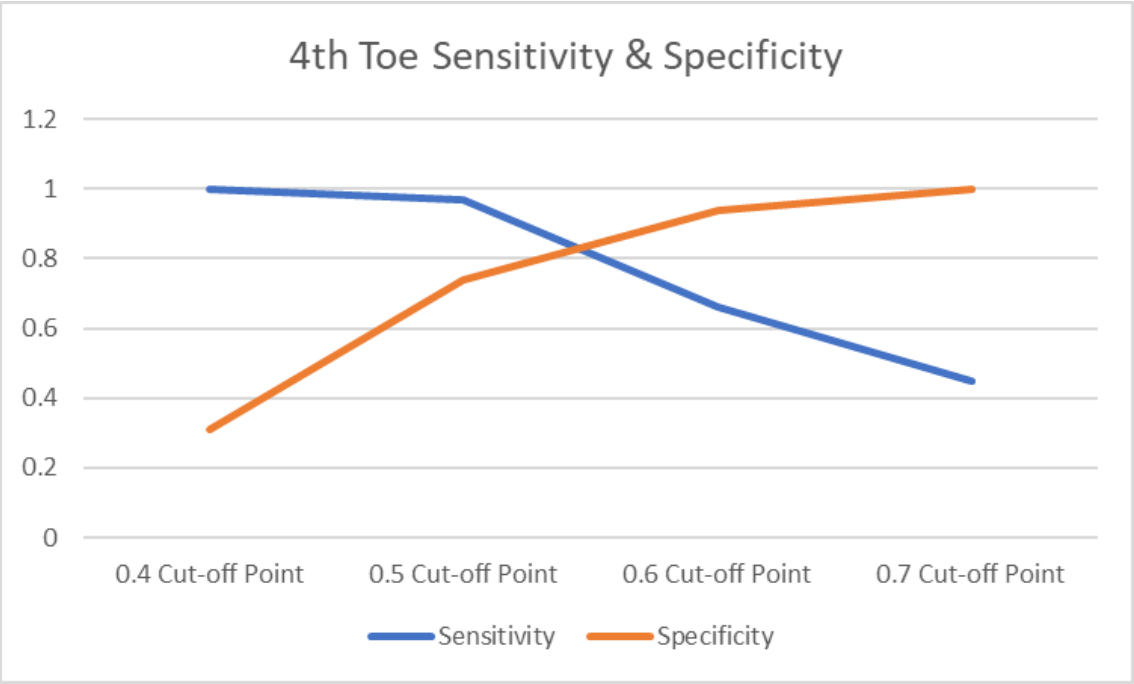

Figure 4.15: Sensitivity & Specificity vs. Probability Graph (4th Toe)

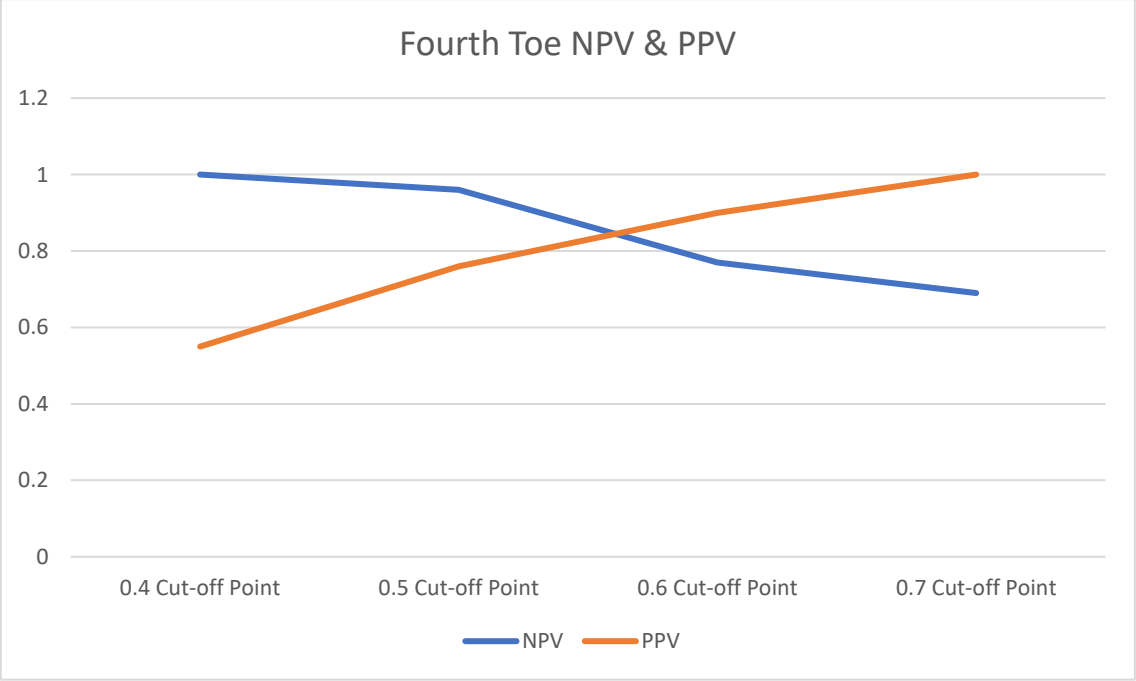

Figure 4.16: Negative Predictive Value vs. Positive Predictive Value Graph (4th Toe)

Analysis of 5th Toe Temperatures

5th Toe (0.4 cut-off point)		Actual Outcome		
		No Complications Present	Complications Present	Total
Predicted Outcome	Less Likely to Have Complications	10	0	10
	More Likely to Have Complications	25	29	54
Total		35	29	64

Table 4:42: Actual vs. Predicted Outcome of 5th Toe ROI (0.4 Probability Cut-off Point)

Specificity	10/35=0.29	Sensitivity	29/29=1
NPV	10/10=1	PPV	29/54=0.54

Table 4:43: Results of 5th Toe ROI (0.4 Probability Cut-off Point)

5th Toe (0.5 cut-off point)		Actual Outcome		
		No Complications Present	Complications Present	Total
Predicted Outcome	Less Likely to Have Complications	28	2	30
	More Likely to Have Complications	7	27	34
Total		35	29	64

Table 4:44: Actual vs. Predicted Outcome of 5th Toe ROI (0.5 Probability Cut-off Point)

Specificity	28/35=0.8	Sensitivity	27/29=0.93
NPV	28/30=0.93	PPV	27/34=0.79

Table 4:45: Results of 5th Toe ROI (0.5 Probability Cut-off Point)

5th Toe (0.6 cut-off point)		Actual Outcome		
		No Complications Present	Complications Present	Total
Predicted Outcome	Less Likely to Have Complications	32	12	44
	More Likely to Have Complications	3	17	20
Total		35	29	64

Table 4:46: Actual vs. Predicted Outcome of 5th Toe ROI (0.6 Probability Cut-off Point)

Specificity	32/35=0.91	Sensitivity	17/29=0.59
NPV	32/44=0.73	PPV	17/20=0.85

Table 4:47: Results of 5th Toe ROI (0.6 Probability Cut-off Point)

5th Toe (0.7 cut-off point)		Actual Outcome		
		No Complications Present	Complications Present	Total
Predicted Outcome	Less Likely to Have Complications	35	17	52
	More Likely to Have Complications	0	12	12
Total		35	29	64

Table 4:48: Actual vs. Predicted Outcome of 5th Toe ROI (0.7 Probability Cut-off Point)

Specificity	35/35=1	Sensitivity	12/29=0.41
NPV	35/52=0.67	PPV	12/12=1

Table 4:49: Results of 5th Toe ROI (0.7 Probability Cut-off Point)

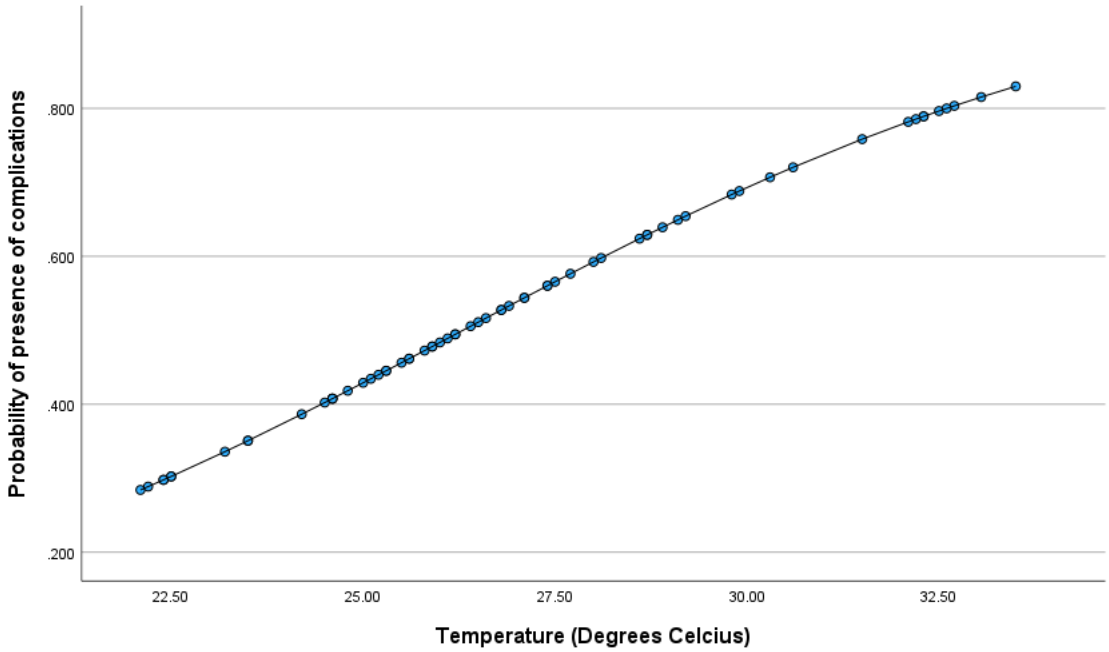

Figure 4.17: Probability of Complications against Temperature Graph (5th Toe)

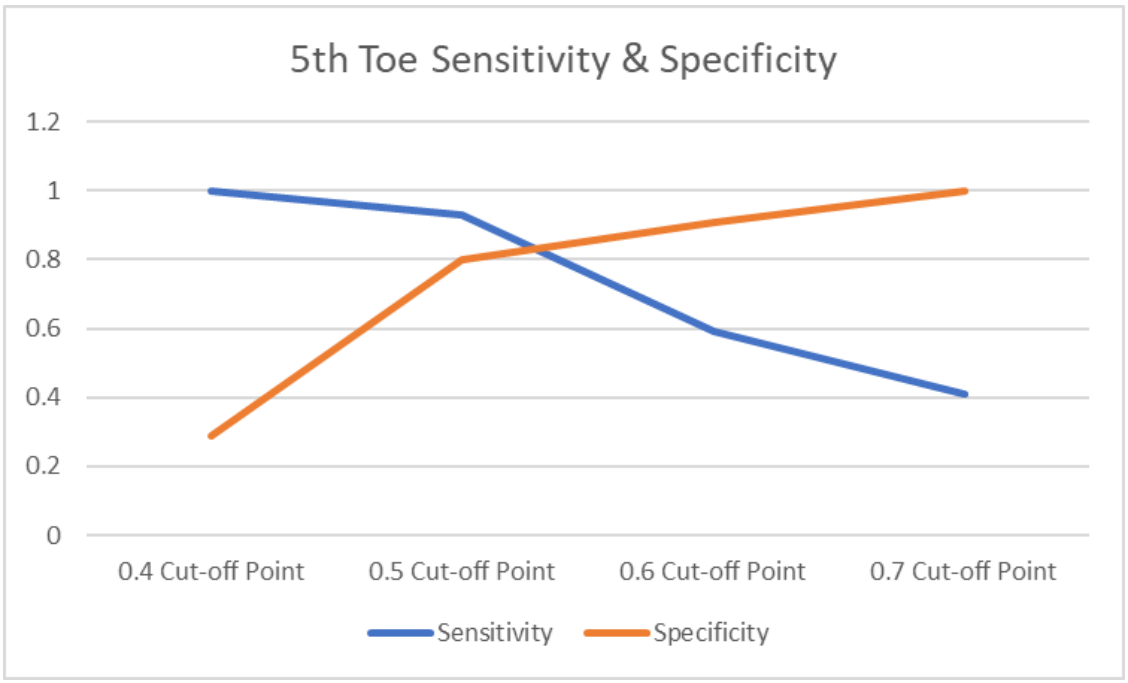

Figure 4.18: Sensitivity & Specificity (5th Toe)

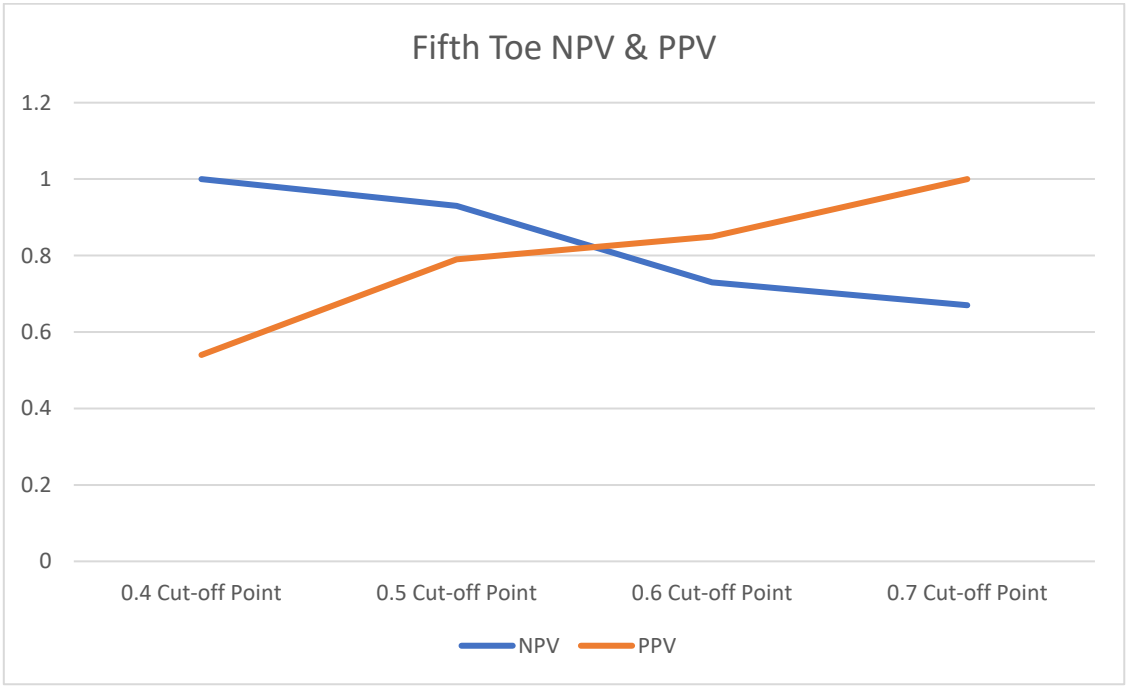

Figure 4.19: Negative Predictive Value &. Positive Predictive Value Graph (5th Toe)

Summary of Sensitivity, Specificity, NPV and PPV of Toes

A summary of the sensitivity and specificity of the toes ROIs for every probability cut-off point can be found in the tables below.

Average Toes

	0.4 Cut-off Point	0.5 Cut-off Point	0.6 Cut-off Point	0.7 Cut-off Point
Sensitivity	1	0.93	0.69	0.38
Specificity	0.37	0.74	0.94	1
NPV	1	0.93	0.71	0.66
PPV	0.58	0.75	0.91	1

Table 4:50: Sensitivity, Specificity, NPV and PPV of Average Toes

1st Toe

	0.4 Cut-off Point	0.5 Cut-off Point	0.6 Cut-off Point	0.7 Cut-off Point
Sensitivity	1	0.93	0.72	0.45
Specificity	0.31	0.69	0.91	1
NPV	1	0.92	0.8	0.69
PPV	0.55	0.71	0.88	1

Table 4:51: Sensitivity, Specificity, NPV and PPV of 1st Toe

2nd Toe

	0.4 Cut-off Point	0.5 Cut-off Point	0.6 Cut-off Point	0.7 Cut-off Point
Sensitivity	1	0.93	0.64	0.43
Specificity	0.43	0.77	0.91	1
NPV	1	0.93	0.76	0.67
PPV	0.58	0.76	0.86	1

Table 4:52: Sensitivity, Specificity, NPV and PPV of 2nd Toe

3rd Toe

	0.4 Cut-off Point	0.5 Cut-off Point	0.6 Cut-off Point	0.7 Cut-off Point
Sensitivity	1	0.93	0.66	0.41
Specificity	0.4	0.77	0.89	1
NPV	1	0.93	0.76	0.67
PPV	0.58	0.77	0.83	1

Table 4:53: Sensitivity, Specificity, NPV and PPV of 3rd Toe

4th Toe

	0.4 Cut-off Point	0.5 Cut-off Point	0.6 Cut-off Point	0.7 Cut-off Point
Sensitivity	1	0.97	0.66	0.45
Specificity	0.31	0.74	0.94	1
NPV	1	0.96	0.77	0.69
PPV	0.55	0.76	0.9	1

Table 4:54: Sensitivity, Specificity, NPV and PPV of 4th Toe

5th Toe

	0.4 Cut-off Point	0.5 Cut-off Point	0.6 Cut-off Point	0.7 Cut-off Point
Sensitivity	1	0.93	0.59	0.41
Specificity	0.29	0.8	0.91	1
NPV	1	0.93	0.73	0.67
PPV	0.54	0.79	0.85	1

Table 4:55: Sensitivity, Specificity, NPV and PPV of 5th Toe

The graphs below demonstrate the sensitivity and specificity of the toes ROIs for every probability cut-off point.

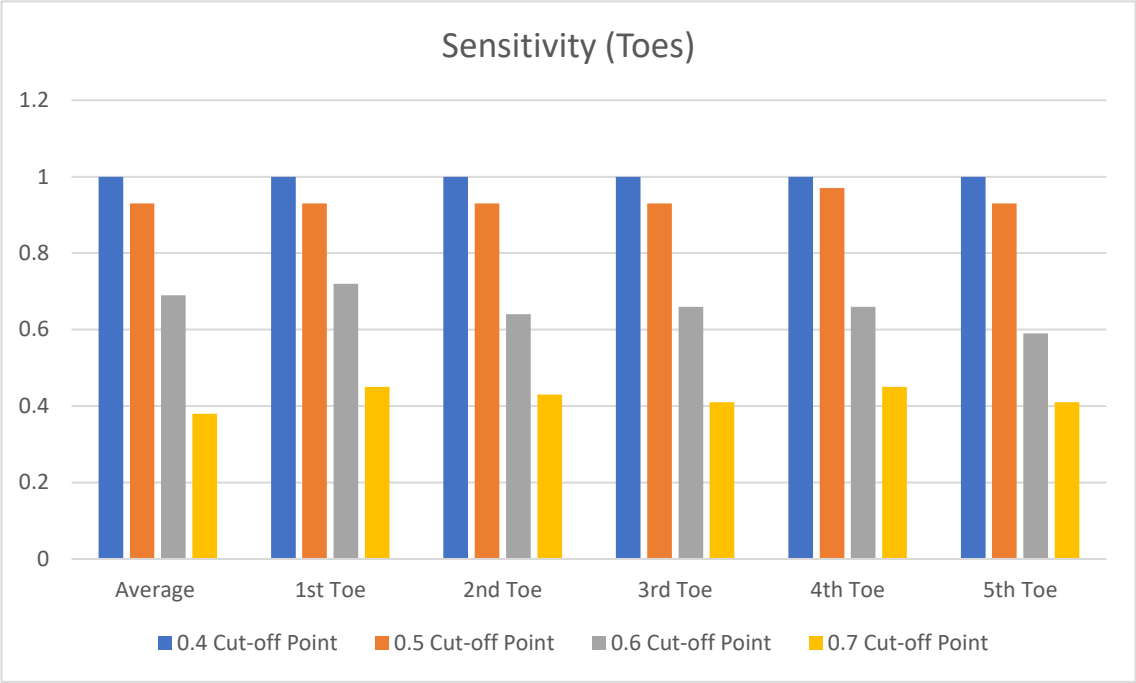

Figure 4.20: Sensitivity of Toes ROIs

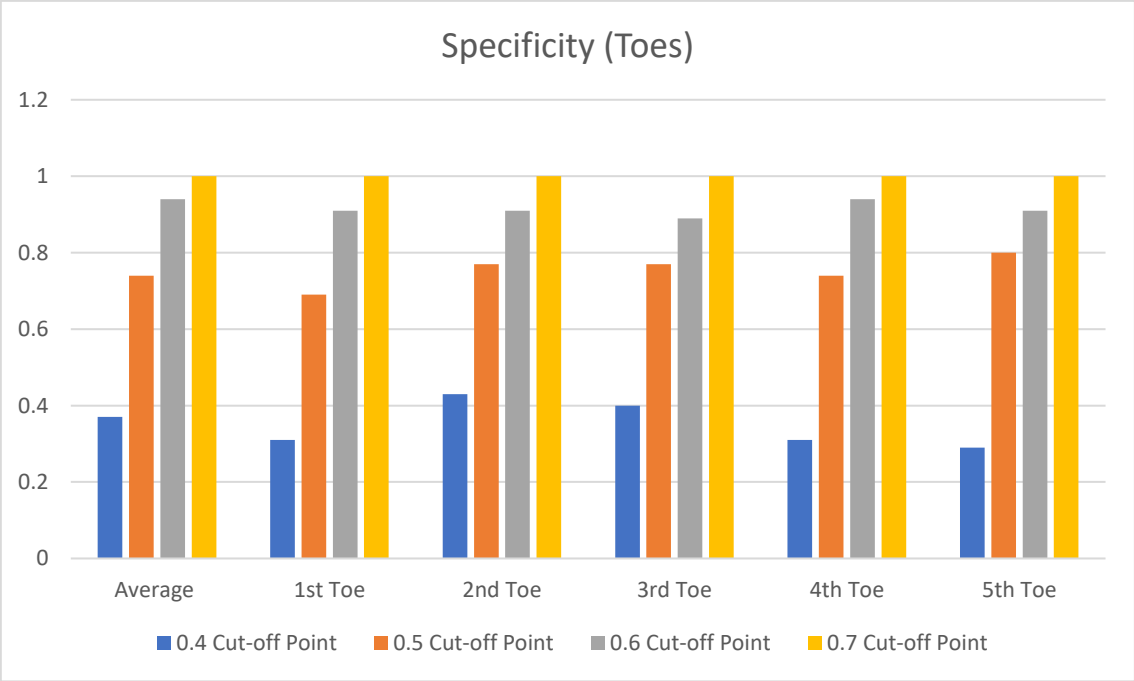

Figure 4.21: Specificity of Toes ROIs

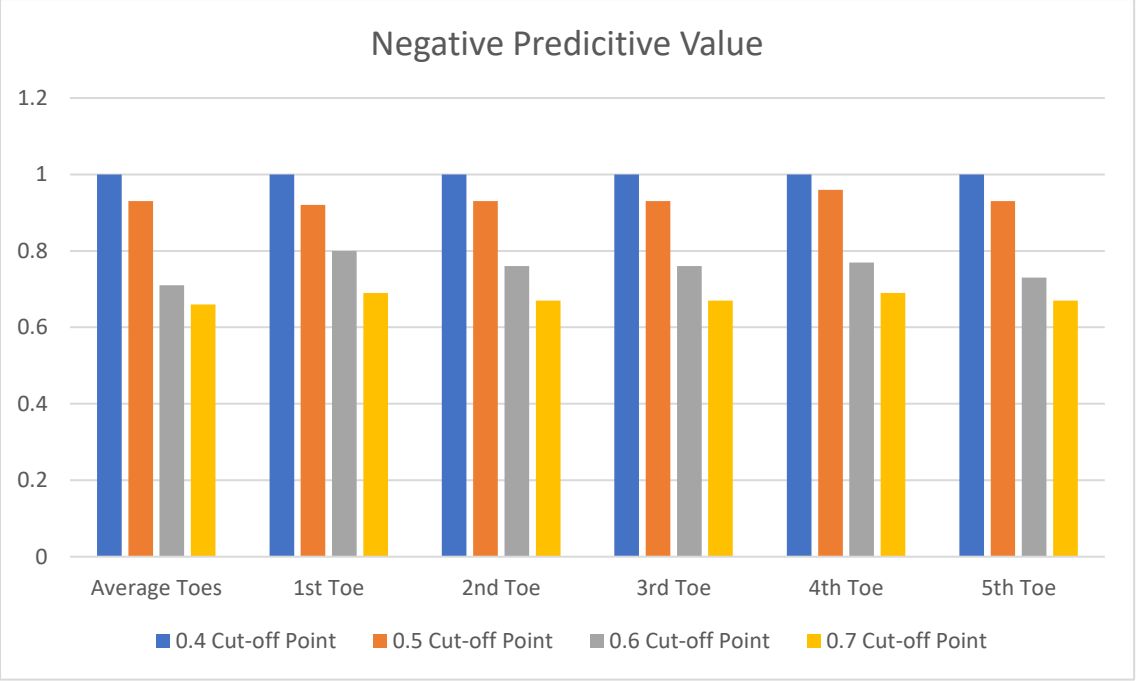

Figure 4.22: NPV of Toes ROIs

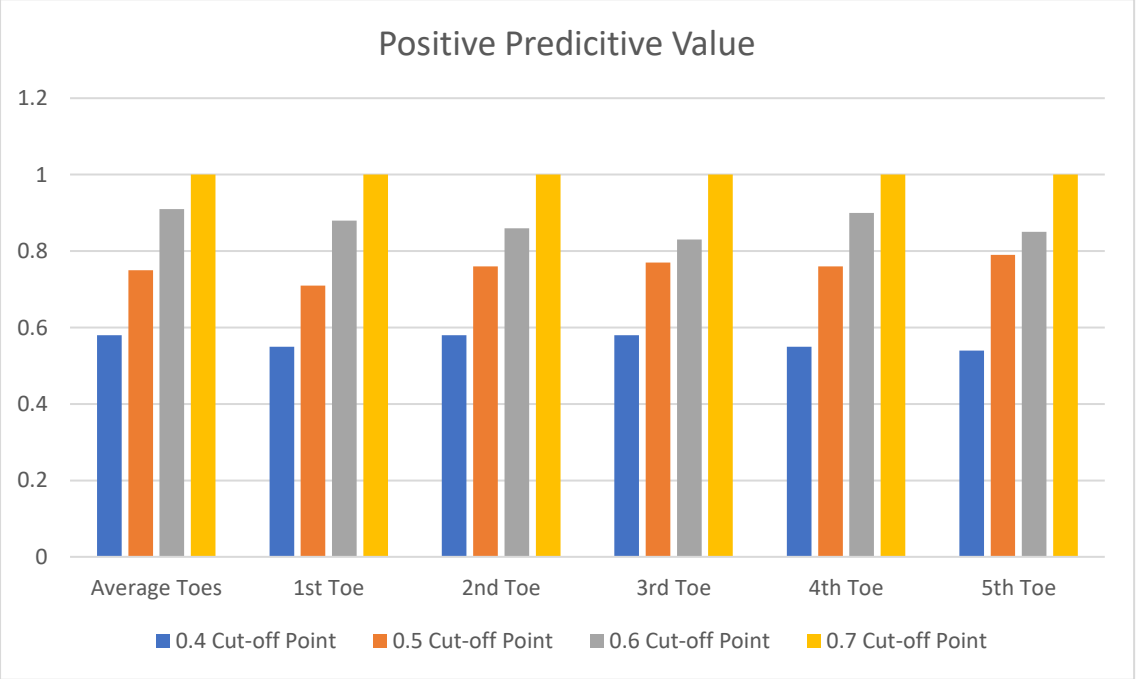

Figure 4.23: PPV of Toes ROIs

Forefoot Temperatures

A different equation than that of the toes was used to determine the probability of T2DM foot complications. This is because the temperatures of the toes are generally lower than those of the forefoot and therefore a separate equation is needed. The first step to determine the probability of T2DM foot complications was to put *p* the as subject of the formula as seen below.

$$\log_e\left(\frac{p}{1-p}\right) = -6.949 + 0.254\text{Temp}$$

$$\frac{p}{1-p} = e^{-6.949+0.254\text{Temp}}$$

$$p = \frac{e^{-6.949+0.254\text{Temp}}}{1+e^{-6.949+0.254\text{Temp}}}$$

The mean temperature of every ROI of the forefoot was inserted into the equation to extract the probability of complications present. Same as what was previously done in the toes, different probability cut-off points were investigated. The predictions were compared with actual diagnosis or exclusion of T2DM foot complications using medically validated tests.

Analysis of Average Forefoot Temperatures

Average Forefoot (0.4 cut-off point)		Actual Outcome		
		No Complications Present	Complications Present	Total
Predicted Outcome	Less Likely to Have Complications	13	0	13
	More Likely to Have Complications	22	29	51
Total		35	29	64

Table 4:56: Actual vs. Predicted Outcome of Average F/F (0.4 Probability Cut-off Point)

Specificity	13/35=0.37	Sensitivity	29/29=1
NPV	13/13=1	PPV	29/51=0.57

Table 4:57: Results of Average F/F ROI (0.4 Probability Cut-off Point)

Average Forefoot (0.5 cut-off point)		Actual Outcome		
		No Complications	Complications Present	Total
Predicted Outcome	Less Likely to Have Complications	21	0	21
	More Likely to Have Complications	14	29	43
Total		35	29	64

Table 4:58: Actual vs. Predicted Outcome of Average F/F (0.5 Probability Cut-off Point)

Specificity	21/35=0.6	Sensitivity	29/29=1
NPV	21/21=1	PPV	29/43=0.67

Table 4:59: Results of Average F/F ROI (0.5 Probability Cut-off Point)

Average Forefoot (0.6 cut-off point)		Actual Outcome		
		No Complications Present	Complications Present	Total
Predicted Outcome	Less Likely to Have Complications	28	8	36
	More Likely to Have Complications	7	21	28
Total		35	29	64

Table 4:60: Actual vs. Predicted Outcome of Average F/F (0.6 Probability Cut-off Point)

Specificity	28/35=0.8	Sensitivity	21/29=0.72
NPV	28/36=0.77	PPV	21/28=0.75

Table 4:61: Results of Average F/F ROI (0.6 Probability Cut-off Point)

Average Forefoot (0.7 cut-off point)		Actual Outcome		
		No Complications Present	Complications Present	Total
Predicted Outcome	Less Likely to Have Complications	34	13	47
	More Likely to Have Complications	1	16	17
Total		35	29	64

Table 4:62: Actual vs. Predicted Outcome of Average F/F (0.7 Probability Cut-off Point)

Specificity	34/35=0.97	Sensitivity	16/29=0.55
NPV	34/47=0.72	PPV	16/17=0.94

Table 4:63: Results of Average F/F ROI (0.7 Probability Cut-off Point)

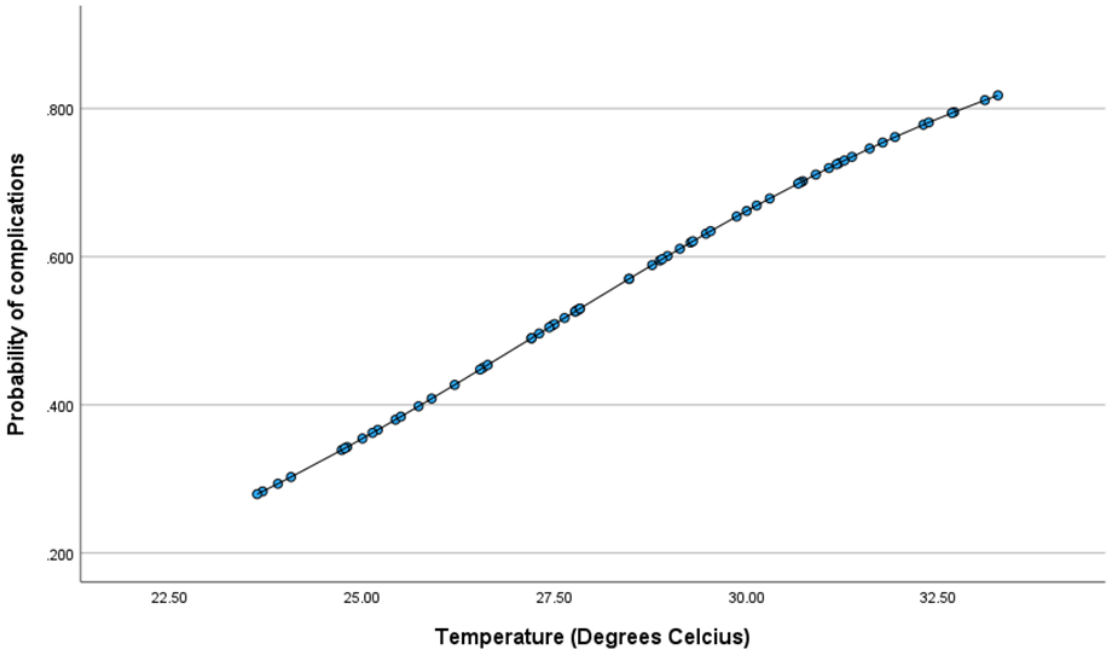

Figure 4.24: Probability of complications against temperature graph (Average Forefoot)

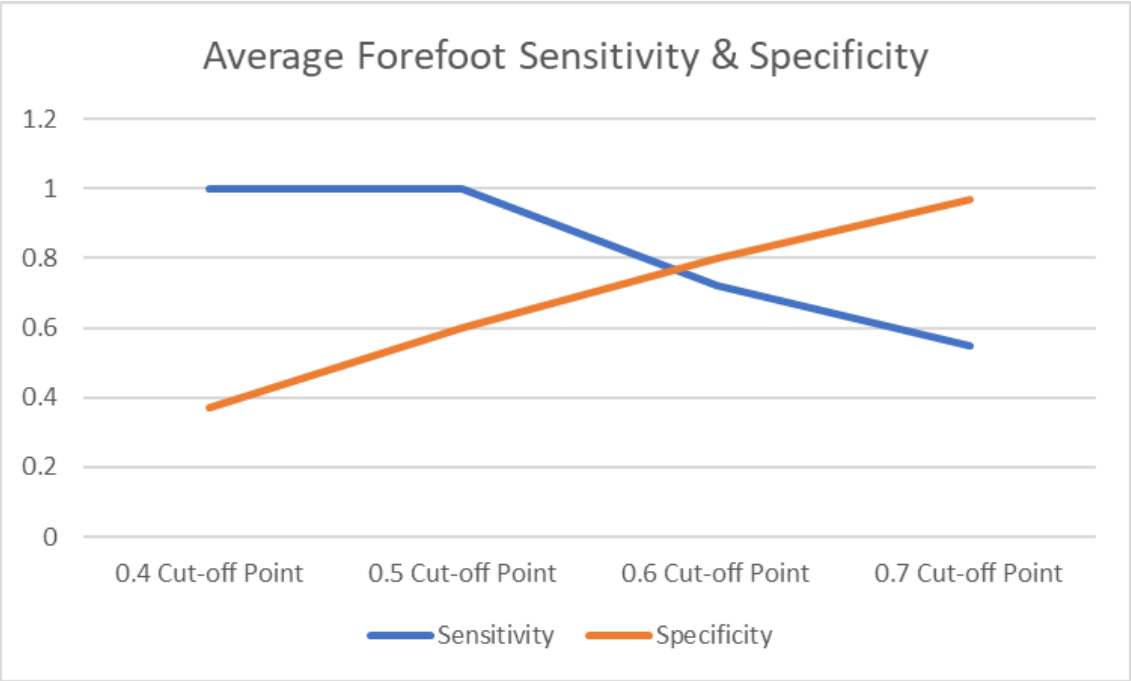

Figure 4.25: Sensitivity and Specificity (Average Forefoot)

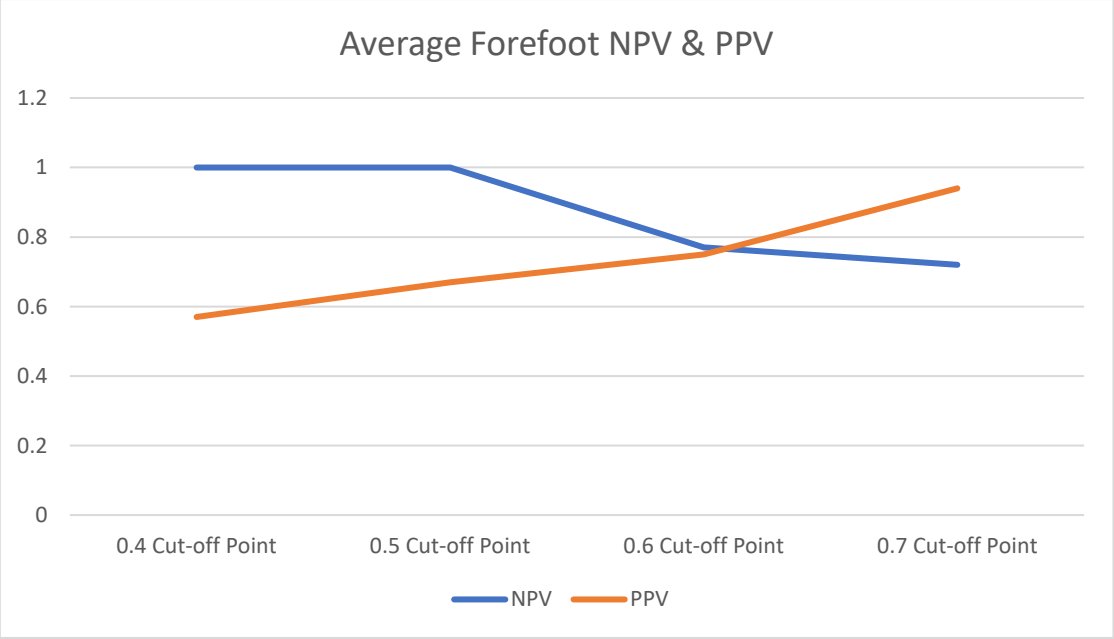

Figure 4.26: NPV & PPV (Average Forefoot)

Analysis of 1st MTH Temperatures

1st MTH (0.4 cut-off point)		Actual Outcome		
		No Complications Present	Complications Present	Total
Predicted Outcome	Less Likely to Have Complications	10	0	10
	More Likely to Have Complications	25	29	54
Total		35	29	64

Table 4:64: Actual vs. Predicted Outcome of 1st MTH ROI (0.4 Probability Cut-off Point)

Specificity	10/35=0.29	Sensitivity	29/29=1
NPV	10/10=1	PPV	29/54=0.54

Table 4:65: Results of 1st MTH ROI (0.4 Probability Cut-off Point)

1st MTH (0.5 cut-off point)		Actual Outcome		
		No Complications Present	Complications Present	Total
Predicted Outcome	Less Likely to Have Complications	19	0	19
	More Likely to Have Complications	16	29	45
Total		35	29	64

Table 4:66: Actual vs. Predicted Outcome of 1st MTH ROI (0.5 Probability Cut-off Point)

Specificity	19/35=0.54	Sensitivity	29/29=1
NPV	19/19=1	PPV	29/45=0.64

Table 4:67: Results of 1st MTH ROI (0.5 Probability Cut-off Point)

1st MTH (0.6 cut-off point)		Actual Outcome		
		No Complications Present	Complications Present	Total
Predicted Outcome	Less Likely to Have Complications	29	7	36
	More Likely to Have Complications	6	22	28
Total		35	29	64

Table 4:68: Actual vs. Predicted Outcome of 1st MTH ROI (0.6 Probability Cut-off Point)

Specificity	29/35=0.83	Sensitivity	22/29=0.76
NPV	29/36=0.81	PPV	22/28=0.79

Table 4:69: Results of 1st MTH ROI (0.6 Probability Cut-off Point)

1st MTH (0.7 cut-off point)		Actual Outcome		
		No Complications Present	Complications Present	Total
Predicted Outcome	Less Likely to Have Complications	34	13	47
	More Likely to Have Complications	1	16	17
Total		35	29	64

Table 4:70: Actual vs. Predicted Outcome of 1st MTH ROI (0.7 Probability Cut-off Point)

Specificity	34/35=0.97	Sensitivity	16/29=0.55
NPV	34/47=0.72	PPV	16/17=0.94

Table 4:71: Results of 1st MTH ROI (0.7 Probability Cut-off Point)

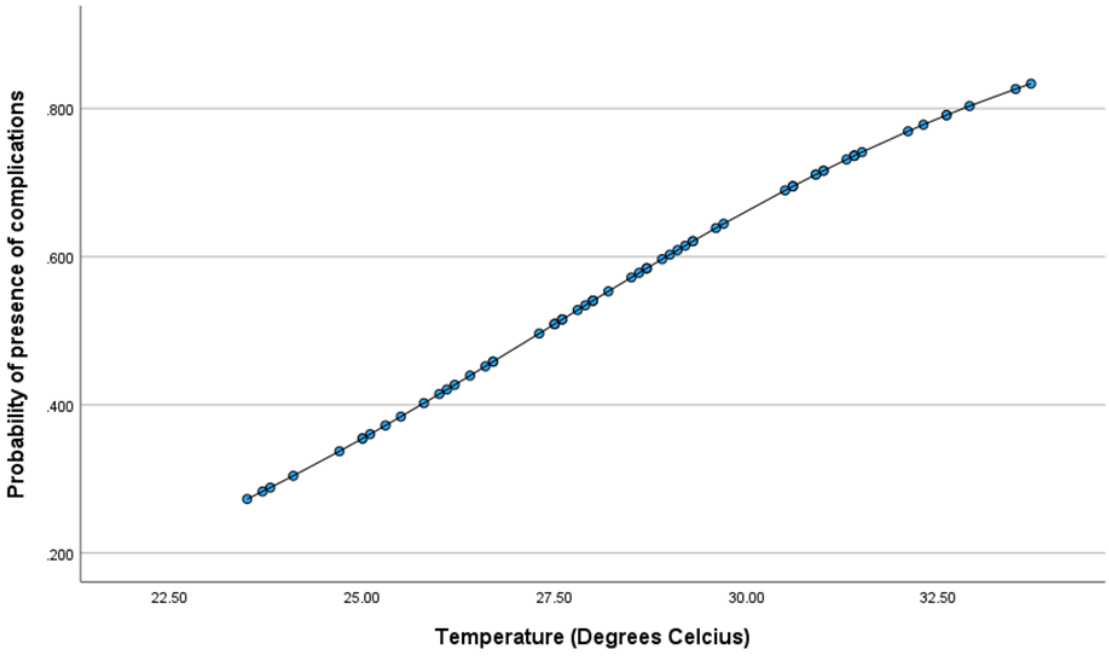

Figure 4.27: Probability of complications against temperature graph (1st MTH)

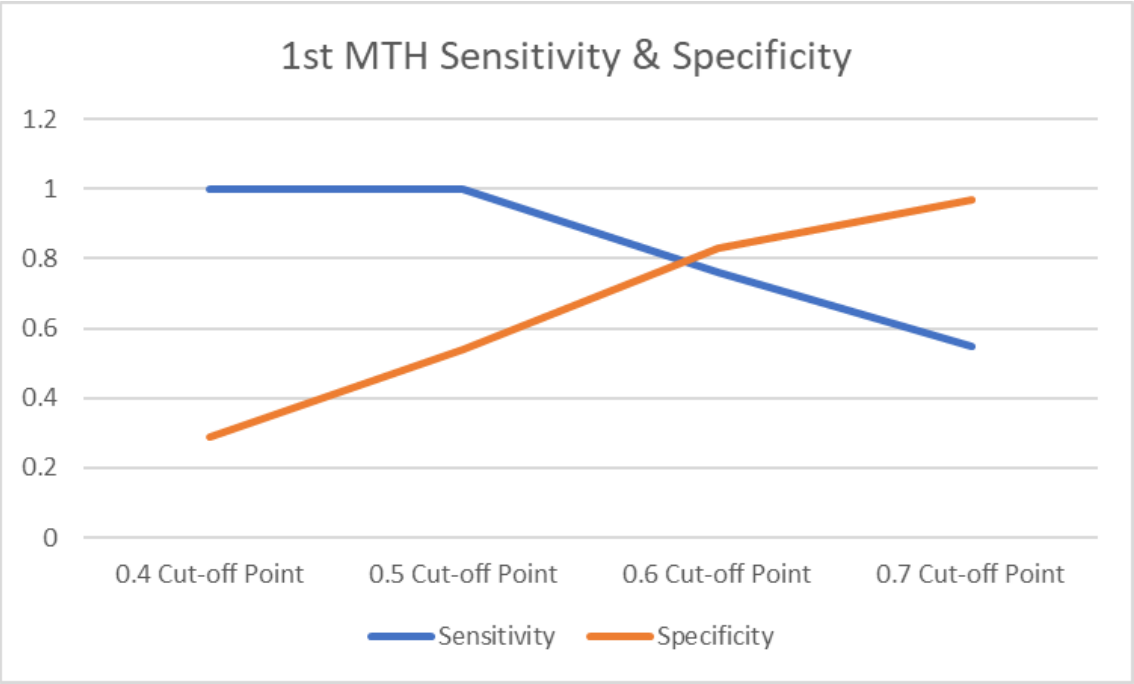

Figure 4.28: Sensitivity & Specificity (1st MTH)

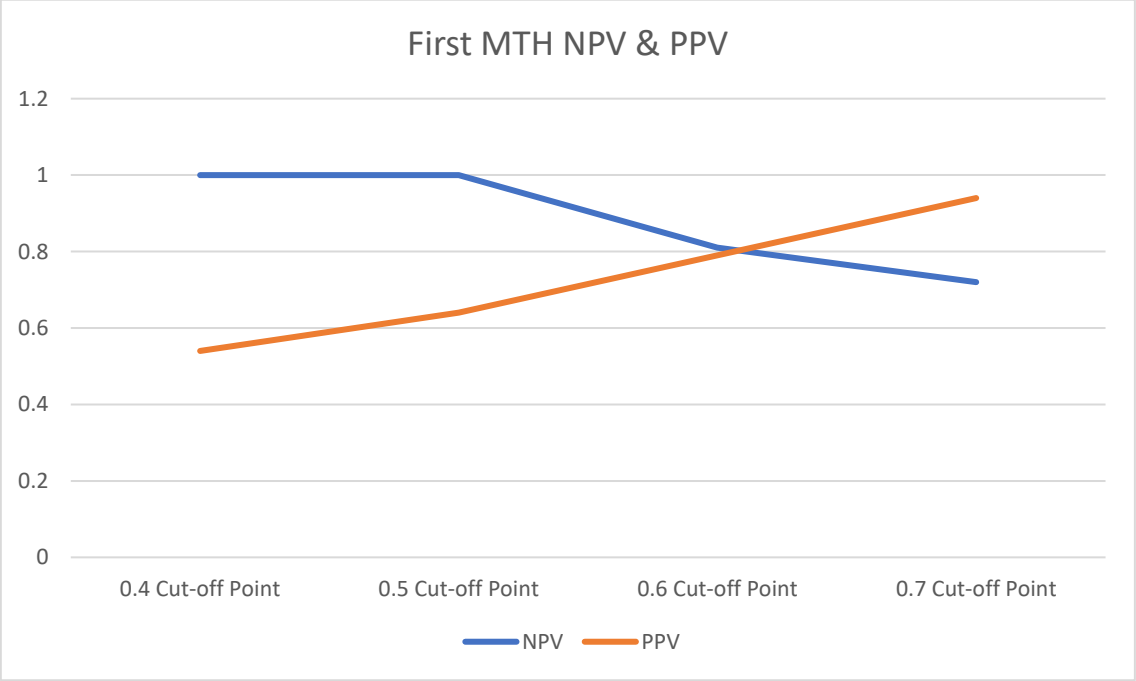

Figure 4.29: NPV & PPV (1st MTH)

Analysis of 3rd MTH Temperatures

3rd MTH (0.4 cut-off point)		Actual Outcome		
		No Complications Present	Complications Present	Total
Predicted Outcome	Less Likely to Have Complications	13	0	13
	More Likely to Have Complications	22	29	51
Total		35	29	64

Table 4:72: Actual vs. Predicted Outcome of 3rd MTH ROI (0.4 Probability Cut-off Point)

Specificity	13/35=0.37	Sensitivity	29/29=1
NPV	13/13=1	PPV	29/51=0.57

Table 4:73: Results of 3rd MTH ROI (0.4 Probability Cut-off Point)

3rd MTH (0.5 cut-off point)		Actual Outcome		
		No Complications Present	Complications Present	Total
Predicted Outcome	Less Likely to Have Complications	19	1	20
	More Likely to Have Complications	16	28	44
Total		35	29	64

Table 4:74: Actual vs. Predicted Outcome of 3rd MTH ROI (0.5 Probability Cut-off Point)

Specificity	19/35=0.54	Sensitivity	28/29=0.97
NPV	19/20=0.95	PPV	0.64

Table 4:75: Results of 3rd MTH ROI (0.5 Probability Cut-off Point)

3rd MTH (0.6 cut-off point)		Actual Outcome		
		No Complications Present	Complications Present	Total
Predicted Outcome	Less Likely to Have Complications	28	7	35
	More Likely to Have Complications	7	22	29
Total		35	29	64

Table 4:76: Actual vs. Predicted Outcome of 3rd MTH ROI (0.6 Probability Cut-off Point)

Specificity	28/35=0.8	Sensitivity	22/29=0.76
NPV	28/35=0.8	PPV	22/29=0.76

Table 4:77: Results of 3rd MTH ROI (0.6 Probability Cut-off Point)

3rd MTH (0.7 cut-off point)		Actual Outcome		
		No Complications Present	Complications Present	Total
Predicted Outcome	Less Likely to Have Complications	34	12	46
	More Likely to Have Complications	1	17	18
Total		35	29	64

Table 4:78: Actual vs. Predicted Outcome of 3rd MTH ROI (0.7 Probability Cut-off Point)

Specificity	34/35=0.97	Sensitivity	17/29=0.59
NPV	34/46=0.74	PPV	17/18=0.94

Table 4:79: Results of 3rd MTH ROI (0.7 Probability Cut-off Point)

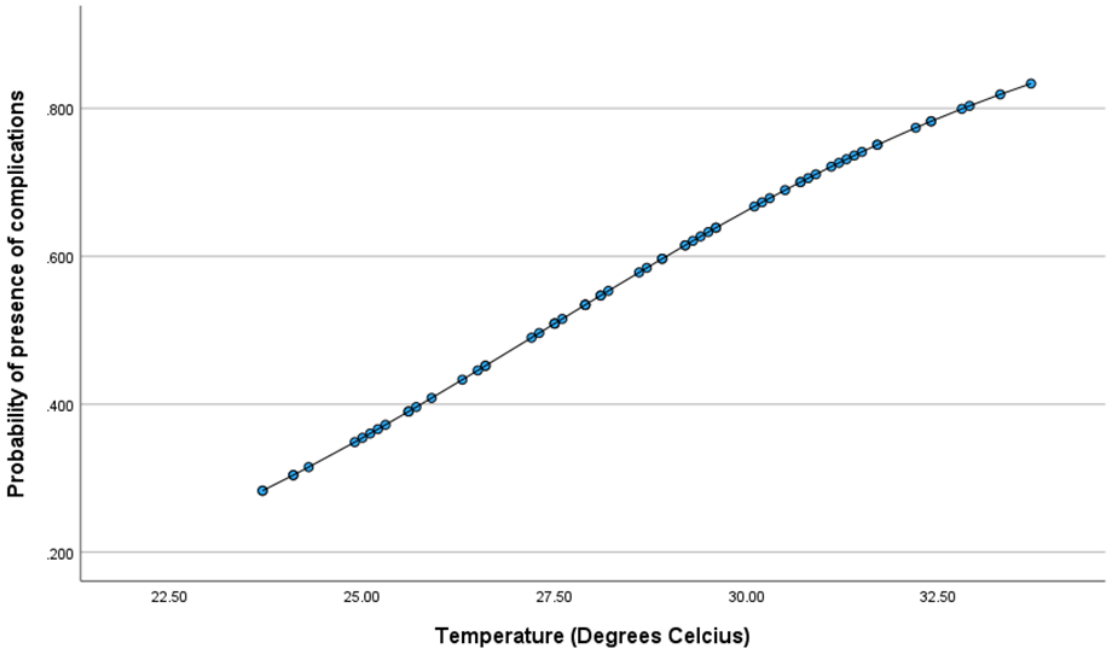

Figure 4.30: Probability of complications against temperature graph (3rd MTH)

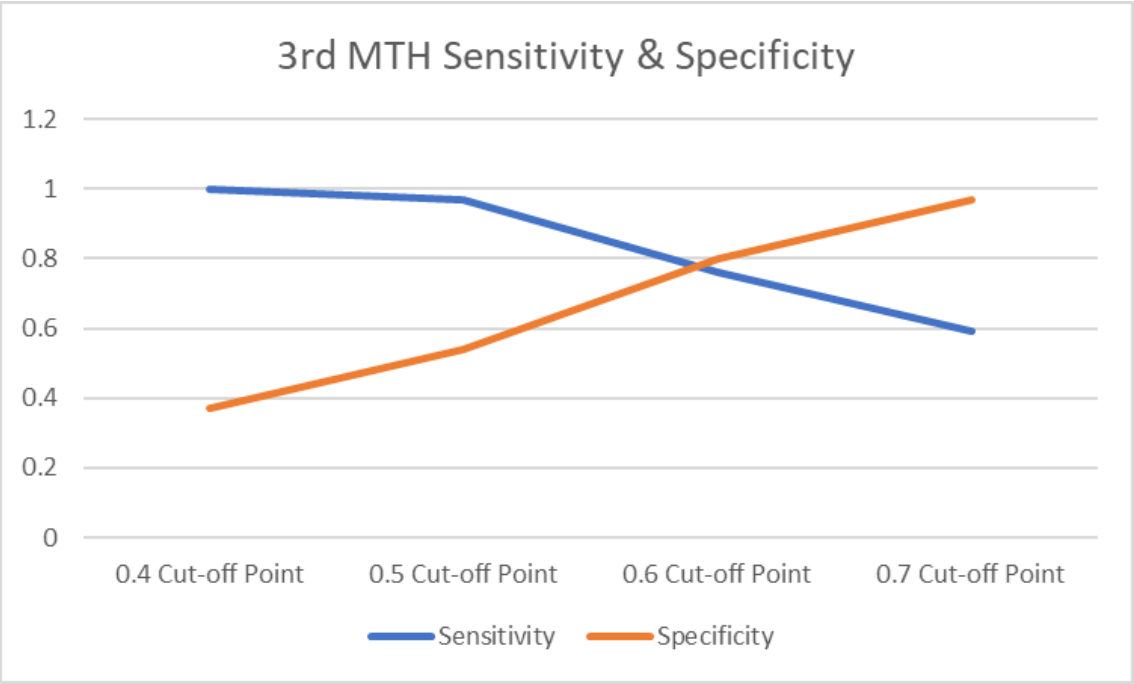

Figure 4.31: Sensitivity & Specificity (3rd MTH)

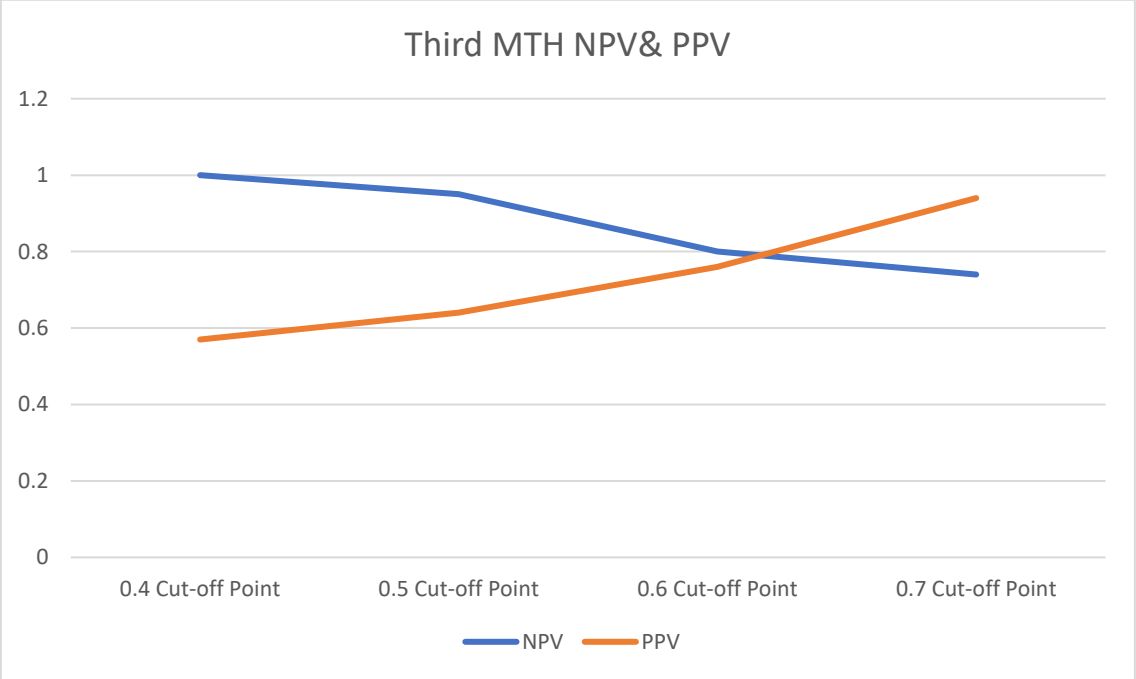

Figure 4.32: NPV & PPV (3rd MTH)

Analysis of 5th MTH Temperatures

5th MTH (0.4 cut-off point)		Actual Outcome		
		No Complications Present	Complications Present	Total
Predicted Outcome	Less Likely to Have Complications	13	0	13
	More Likely to Have Complications	22	29	51
Total		35	29	64

Table 4:80: Actual vs. Predicted Outcome of 5th MTH ROI (0.4 Probability Cut-off Point)

Specificity	13/35=0.37	Sensitivity	29/29=1
NPV	13/13=1	PPV	29/51=0.57

Table 4:81: Results of 5th MTH ROI (0.4 Probability Cut-off Point)

5th MTH (0.5 cut-off point)		Actual Outcome		
		No Complications Present	Complications Present	Total
Predicted Outcome	Less Likely to Have Complications	24	2	26
	More Likely to Have Complications	11	27	38
Total		35	29	64

Table 4:82: Actual vs. Predicted Outcome of 5th MTH ROI (0.5 Probability Cut-off Point)

Specificity	24/35=0.69	Sensitivity	27/29=0.93
NPV	24/26=0.92	PPV	27/38=0.71

Table 4:83: Results of 5th MTH ROI (0.5 Probability Cut-off Point)

5^{th} MTH (0.6 cut-off point)		Actual Outcome		
		No Complications Present	Complications Present	Total
Predicted Outcome	Less Likely to Have Complications	29	8	37
	More Likely to Have Complications	6	21	27
Total		35	29	64

Table 4:84: Actual vs. Predicted Outcome of 5th MTH ROI (0.6 Probability Cut-off Point)

Specificity	29/35=0.83	Sensitivity	21/29=0.72
NPV	29/37=0.78	PPV	21/27=0.78

Table 4:85: Results of 5th MTH ROI (0.6 Probability Cut-off Point)

5^{th} MTH (0.7 cut-off point)		Actual Outcome		
		No Complications Present	Complications Present	Total
Predicted Outcome	Less Likely to Have Complications	35	13	48
	More Likely to Have Complications	0	16	16
Total		35	29	64

Table 4:86: Actual vs. Predicted Outcome of 5th MTH ROI (0.7 Probability Cut-off Point)

Specificity	35/35=1	Sensitivity	16/29=0.55
NPV	35/48=0.73	PPV	16/16=1

Table 4:87: Results of 5th MTH ROI (0.7 Probability Cut-off Point)

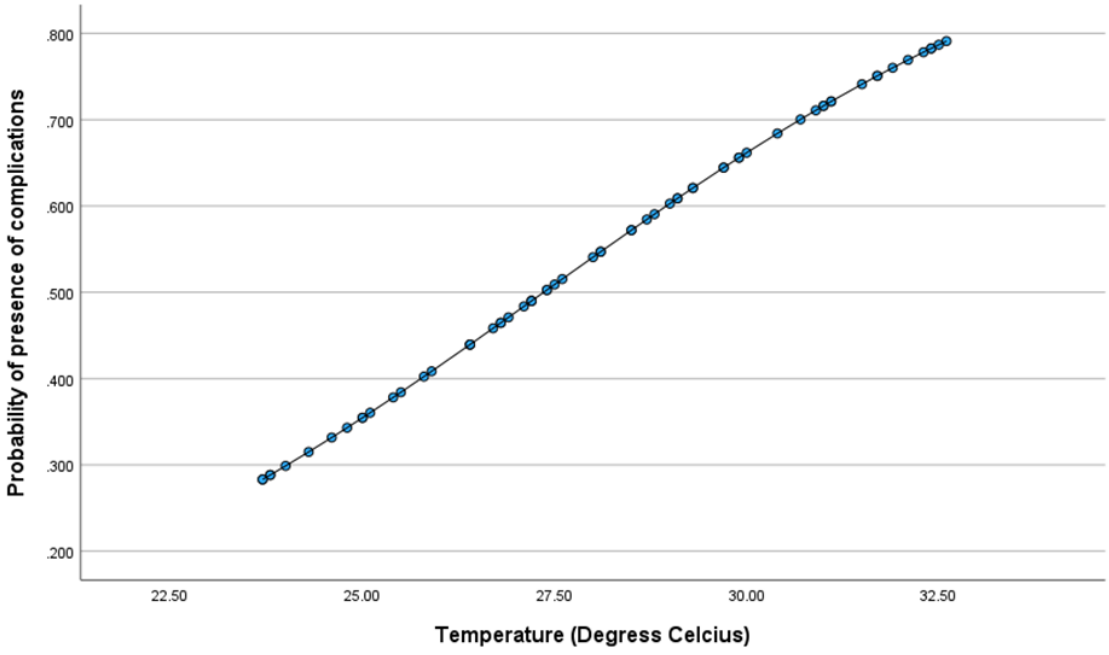

Figure 4.33: Probability of complications against temperature graph (5^{th} MTH)

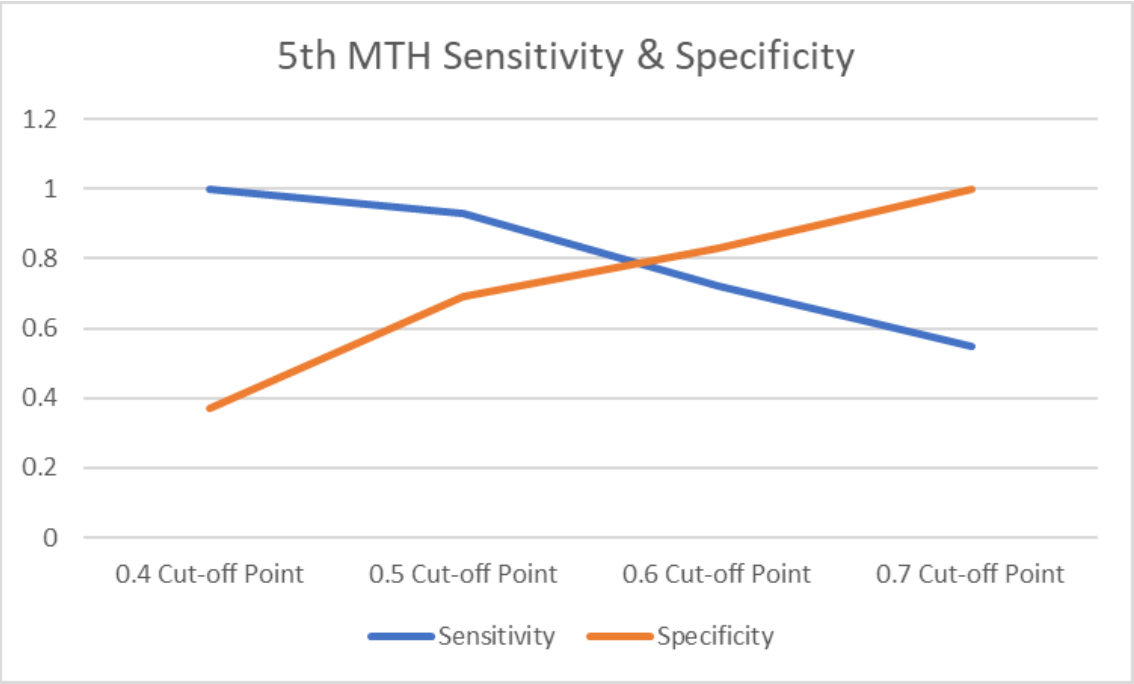

Figure 4.34: Sensitivity & Specificity (5th MTH)

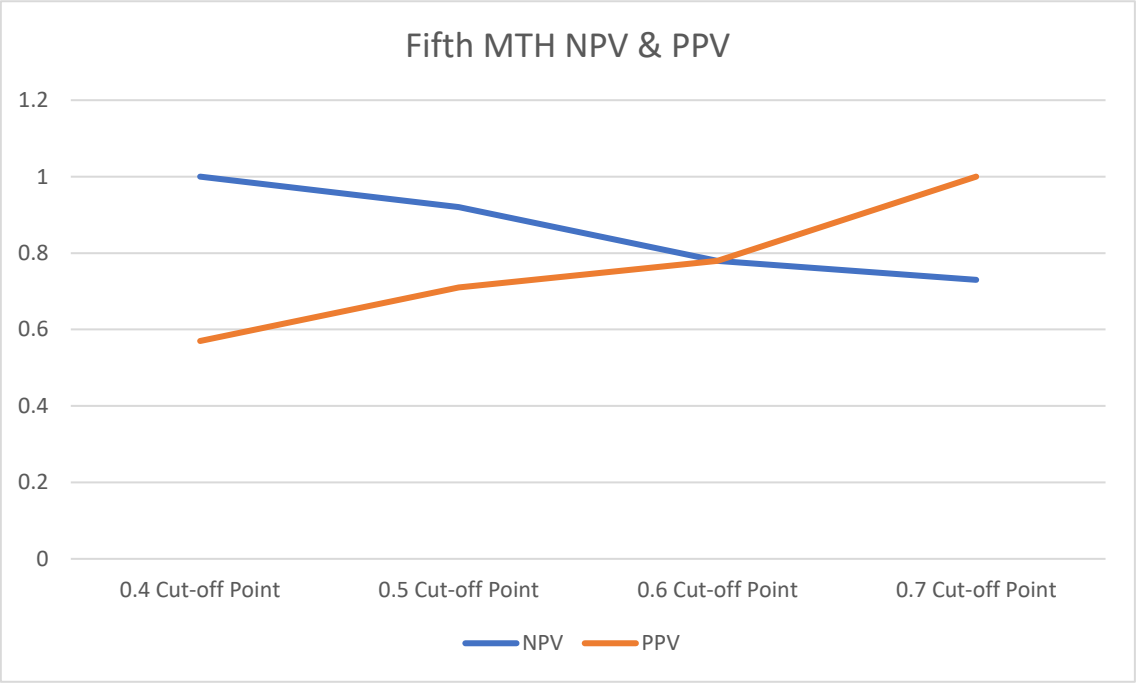

Figure 4.35: NPV & PPV (5th MTH)

Sensitivity, Specificity, NPV & PPV of Forefoot

Average Forefoot

	0.4 Cut-off Point	0.5 Cut-off Point	0.6 Cut-off Point	0.7 Cut-off Point
Sensitivity	1	1	0.72	0.55
Specificity	0.37	0.6	0.8	0.97
NPV	1	1	0.77	0.72
PPV	0.57	0.67	0.75	0.94

Table 4:88: Sensitivity, Specificity, NPV and PPV of Average Forefoot

1st MTH

	0.4 Cut-off Point	0.5 Cut-off Point	0.6 Cut-off Point	0.7 Cut-off Point
Sensitivity	1	1	0.76	0.55
Specificity	0.29	0.54	0.83	0.97
NPV	1	1	0.81	0.72
PPV	0.54	0.64	0.79	0.94

Table 4:89: Sensitivity, Specificity, NPV and PPV of 1st MTH

3rd MTH

	0.4 Cut-off Point	0.5 Cut-off Point	0.6 Cut-off Point	0.7 Cut-off Point
Sensitivity	1	0.97	0.76	0.59
Specificity	0.37	0.54	0.8	0.97
NPV	1	0.95	0.8	0.74
PPV	0.57	0.64	0.76	0.94

Table 4:90: Sensitivity, Specificity, NPV and PPV of 3rd MTH

5th MTH

	0.4 Cut-off Point	0.5 Cut-off Point	0.6 Cut-off Point	0.7 Cut-off Point
Sensitivity	1	0.93	0.72	0.55
Specificity	0.37	0.69	0.83	1
NPV	1	0.92	0.78	0.73
PPV	0.57	0.71	0.78	1

Table 4:91: Sensitivity, Specificity, NPV and PPV of 5th MTH

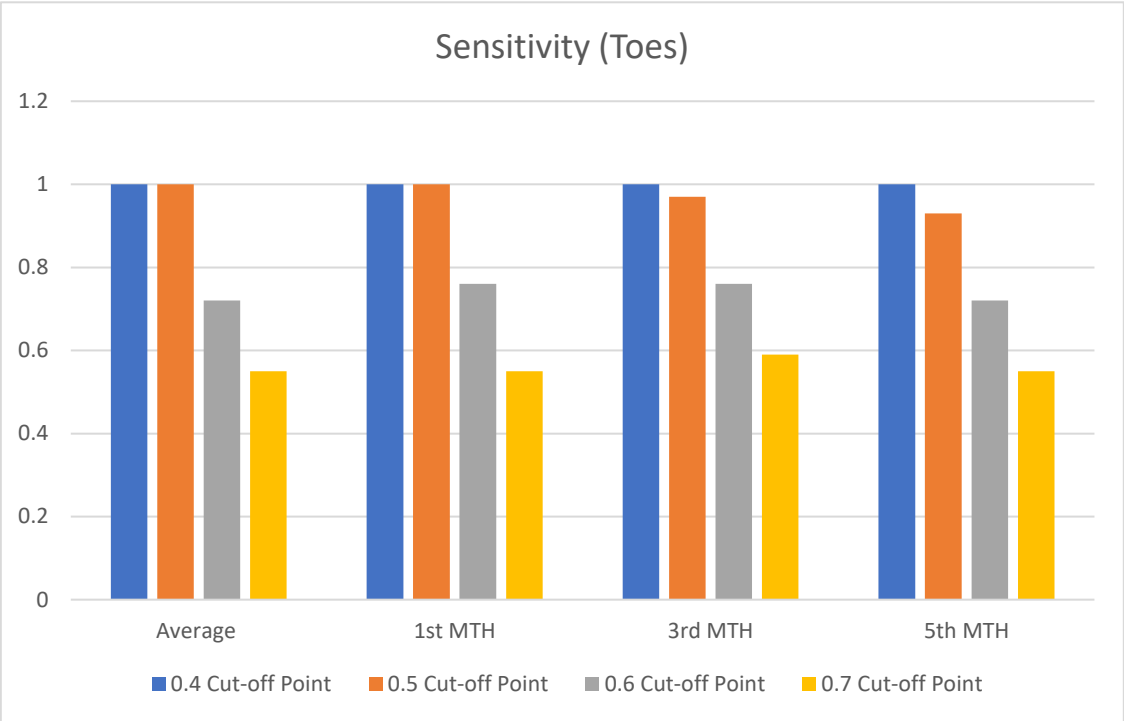

Figure 4.36: Sensitivity of Forefoot ROIs

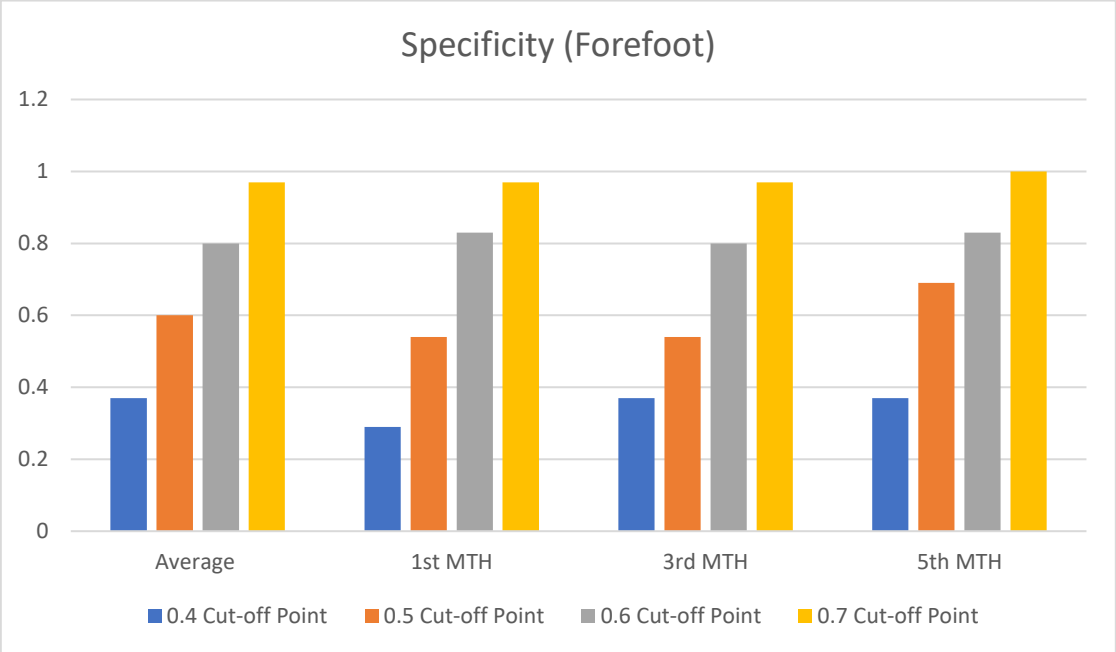

Figure 4.37: Specificity of Forefoot ROIs

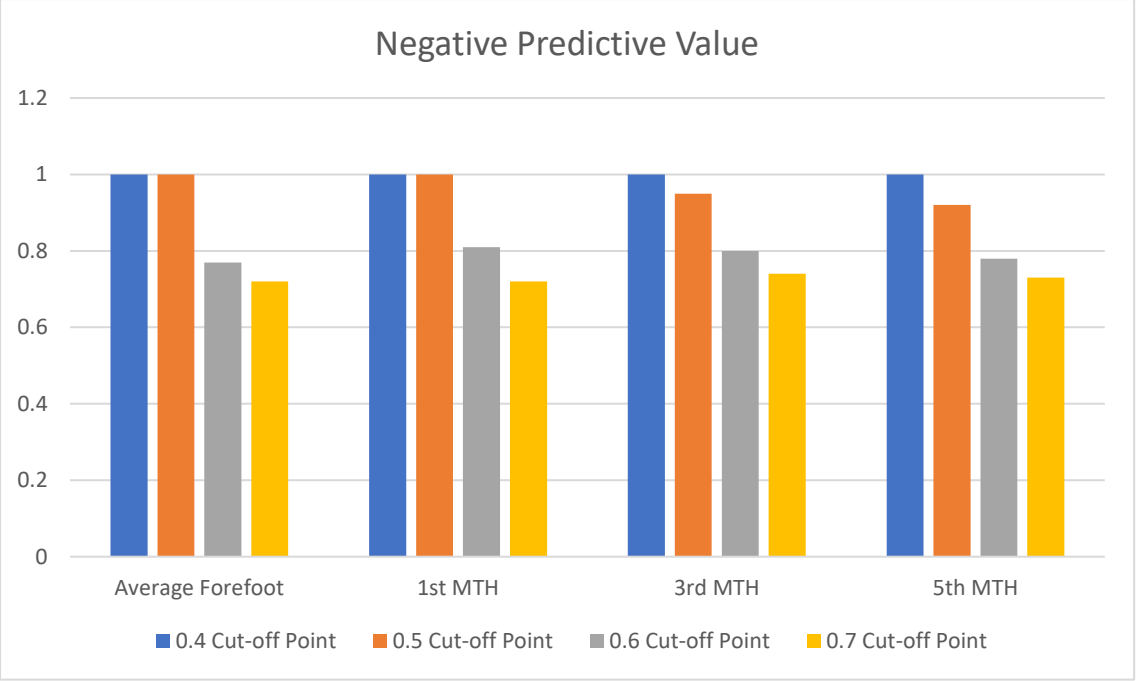

Figure 4.38: NPV of Forefoot ROIs

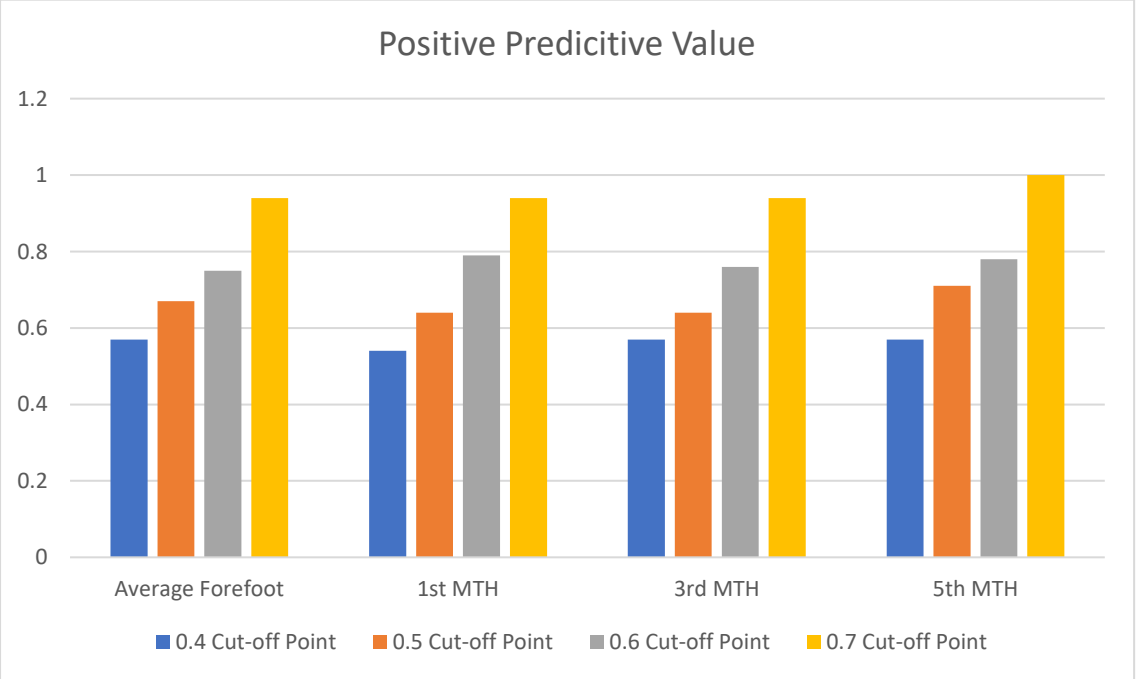

Figure 4.39: PPV of Forefoot ROIs

Additional Data Analysed

Average ROI Temperature for Each Group

Based on the medically validated tests, the mean cutaneous temperatures of each ROI for every group of T2DM complications were determined. The following two graphs show the mean temperatures of toes for those diagnosed as healthy, ischaemic, neuropathic and neuroischaemic.

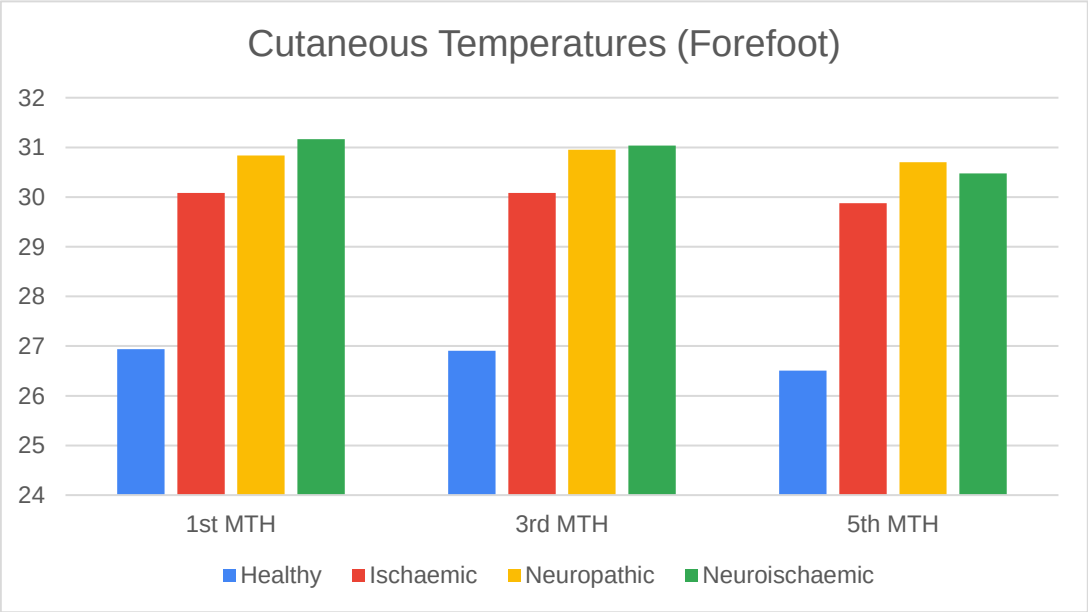

Figure 4.40: Forefoot Cutaneous Temperatures

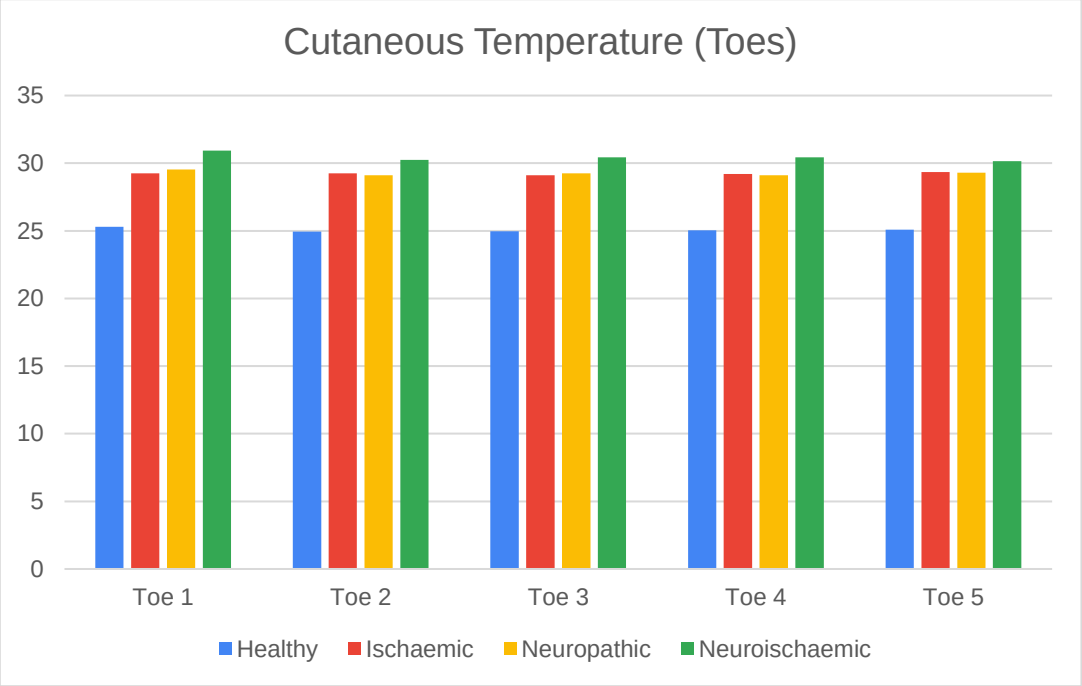

Figure 4.41: Toes Cutaneous Temperatures

	Mean Forefoot ROI Temperatures	Mean Toe ROI Temperatures
Healthy	26.78	25.06
Ischaemic	30.01	29.23
Neuropathic	30.83	29.26
Neuroischaemic	30.89	30.44

Table 4:92: Mean Temperatures

These results show that the mean cutaneous plantar foot temperature in all the three different T2DM groups is higher than those of healthy T2DM participants. The highest mean temperature was recorded in participants with neuroischaemia in nearly all the ROI except the 5th MTH where participants with neuropathy only had the highest mean temperatures. Furthermore, similar temperatures between the three T2DM complications groups were recorded in both the toes and forefoot ROI.

Comparing Mean Temperatures Between the Four Different Groups

Shapiro-Wilk Test was used to test for normality of data.

	Statistic	df	Sig.
Hallux	0.964	64	0.085
Second Toe	0.961	63	0.045
Third Toe	0.960	64	0.034
Fourth Toe	0.957	64	0.026
Fifth Toe	0.951	64	0.013
First MTH	0.978	64	0.293
Third MTH	0.974	64	0.190
Fifth MTH	0.958	64	0.030

Table 4:93: Shapiro-Wilk Test

Data in the Hallux, 1st MTH and 5th MTH ROIs was found to be normally distributed as the p-value exceeded the 0.05 level of significance. Data in the other five ROIs was considered to be non-normally distributed since the p-value did not exceed the 0.05 level of significance.

Comparing Mean Temperatures Between the Four Different Groups

To determine if there is any statistically significant difference between the four different groups of T2DM foot complications in normally distributed data, a one-way ANOVA with post-hoc Tukey test was done.

Null Hypothesis: There is no statistically significant difference in mean cutaneous temperature of the foot between healthy participants and those with T2DM foot complications.

Alternative Hypothesis: There is a statistically significant difference in mean cutaneous temperature of the foot between healthy participants and those with T2DM foot complications.

		Sum of Squares	Mean Square	F	Sig.
Hallux	Between Groups	336.037	112.012	22.888	<.001
	Within Groups	293.642	4.894		
	Total	629.679			
First MTH	Between Groups	220.602	73.534	20.592	<.001
	Within Groups	214.257	3.571		
	Total	434.859			
Third MTH	Between Groups	224.670	74.890	20.156	<.001
	Within Groups	222.927	3.715		
	Total	447.597			

Table 4:94: One-way ANOVA

Since the p-values are less than the 0.05 level of significance, the null hypothesis is rejected and therefore this test shows that there is a statistically significant difference in mean cutaneous temperature of the foot between healthy participants and those with T2DM foot complications. Post-hoc Tukey test was done to identify between which groups there is statistically significant difference in cutaneous temperature.

Multiple Comparisons							
Tukey HSD							
Dependent Variable	Group	Group	Mean Difference	Std. Error	Sig.	95% Confidence Interval	
						Lower Bound	Upper Bound
Hallux	Healthy	Ischaemic	-3.95286*	.74004	<.001	-5.9084	-1.9973
		Neuropathic	-4.24730*	.82681	<.001	-6.4322	-2.0624
		Neuroischaemic	-5.62161*	.86694	<.001	-7.9125	-3.3307
	Ischaemic	Healthy	3.95286*	.74004	<.001	1.9973	5.9084
		Neuropathic	-.29444	.97551	.990	-2.8722	2.2834
		Neuroischaemic	-1.66875	1.00975	.358	-4.3370	.9995
	Neuropathic	Healthy	4.24730*	.82681	<.001	2.0624	6.4322
		Ischaemic	.29444	.97551	.990	-2.2834	2.8722
		Neuroischaemic	-1.37431	1.07496	.580	-4.2149	1.4663
	Neuroischaemic	Healthy	5.62161*	.86694	<.001	3.3307	7.9125
		Ischaemic	1.66875	1.00975	.358	-.9995	4.3370
		Neuropathic	1.37431	1.07496	.580	-1.4663	4.2149
1st MTH	Healthy	Ischaemic	-3.14619*	.63214	<.001	-4.8166	-1.4757
		Neuropathic	-3.89619*	.70626	<.001	-5.7625	-2.0299
		Neuroischaemic	-4.22536*	.74054	<.001	-6.1822	-2.2685
	Ischaemic	Healthy	3.14619*	.63214	<.001	1.4757	4.8166
		Neuropathic	-.75000	.83328	.805	-2.9520	1.4520
		Neuroischaemic	-1.07917	.86252	.597	-3.3584	1.2001
	Neuropathic	Healthy	3.89619*	.70626	<.001	2.0299	5.7625
		Ischaemic	.75000	.83328	.805	-1.4520	2.9520
		Neuroischaemic	-.32917	.91823	.984	-2.7556	2.0973
	Neuroischaemic	Healthy	4.22536*	.74054	<.001	2.2685	6.1822
		Ischaemic	1.07917	.86252	.597	-1.2001	3.3584
		Neuropathic	.32917	.91823	.984	-2.0973	2.7556

3rd MTH	Healthy	Ischaemic	-3.18048*	.64481	<.001	-4.8844	-1.4766
		Neuropathic	-4.05270*	.72041	<.001	-5.9564	-2.1490
		Neuroischaemic	-4.13464*	.75537	<.001	-6.1307	-2.1386
	Ischaemic	Healthy	3.18048*	.64481	<.001	1.4766	4.8844
		Neuropathic	-.87222	.84997	.735	-3.1183	1.3738
		Neuroischaemic	-.95417	.87980	.700	-3.2791	1.3707
	Neuropathic	Healthy	4.05270*	.72041	<.001	2.1490	5.9564
		Ischaemic	.87222	.84997	.735	-1.3738	3.1183
		Neuroischaemic	-.08194	.93662	1.000	-2.5570	2.3931
	Neuroischaemic	Healthy	4.13464*	.75537	<.001	2.1386	6.1307
		Ischaemic	.95417	.87980	.700	-1.3707	3.2791
		Neuropathic	.08194	.93662	1.000	-2.3931	2.5570

Table 4:95: Post-Hoc Tukey Test

For data, which was not normally distributed, the Kruskal-Wallis Test was used to determine whether there is any statistically significant difference in mean foot temperatures between the four different groups.

Hypothesis Test Summary				
	Null Hypothesis	Test	Sig.a,b	Decision
1	The distribution of Second Toe is the same across categories of	Independent-Samples Kruskal-Wallis Test	<.001	Reject the null hypothesis.
2	The distribution of Third Toe is the same across categories of	Independent-Samples Kruskal-Wallis Test	<.001	Reject the null hypothesis.
3	The distribution of Fourth Toe is the same across categories of	Independent-Samples Kruskal-Wallis Test	<.001	Reject the null hypothesis.
4	The distribution of Fifth Toe is the same across categories of Group.	Independent-Samples Kruskal-Wallis Test	<.001	Reject the null hypothesis.
5	The distribution of Fifth MTH is the same across categories of	Independent-Samples Kruskal-Wallis Test	<.001	Reject the null hypothesis.

Table 4:96: Kruskal-Wallis Test

Second Toe				
	Test Statistic	Std. Error	Std. Test Statistic	Sig.
Healthy-Ischaemic	-25.079	6.335	-3.959	<.001
Healthy-Neuropathic	-25.832	6.850	-3.771	<.001
Healthy-Neuroischaemic	-30.505	7.182	-4.247	<.001
Ischaemic-Neuropathic	-.753	8.238	-.091	.927
Ischaemic-Neuroischaemic	-5.426	8.516	-.637	.524
Neuropathic-Neuroischaemic	-4.674	8.906	-.525	.600

Table 4:97: Kruskal-Wallis Test (Second toe ROI)

Third Toe				
	Test Statistic	Std. Error	Std. Test Statistic	Sig.
Healthy-Ischaemic	-25.546	6.227	-4.102	<.001
Healthy-Neuropathic	-27.727	6.957	-3.985	<.001
Healthy-Neuroischaemic	-31.859	7.295	-4.367	<.001
Ischaemic-Neuropathic	-2.181	8.209	-.266	.791
Ischaemic-Neuroischaemic	-6.313	8.497	-.743	.458
Neuropathic-Neuroischaemic	-4.132	9.045	-.457	.648

Table 4:98: Kruskal-Wallis Test (Third toe ROI)

Fourth Toe				
	Test Statistic	Std. Error	Std. Test Statistic	Sig.
Healthy-Ischaemic	-25.980	6.227	-4.172	<.001
Healthy-Neuropathic	-27.271	6.957	-3.920	<.001
Healthy-Neuroischaemic	-32.521	7.295	-4.458	<.001
Ischaemic-Neuropathic	-1.292	8.209	-.157	.875
Ischaemic-Neuroischaemic	-6.542	8.497	-.770	.441
Neuropathic-Neuroischaemic	-5.250	9.045	-.580	.562

Table 4:99: Kruskal-Wallis Test (Fourth toe ROI)

Fifth Toe				
	Test Statistic	Std. Error	Std. Test Statistic	Sig.
Healthy-Ischaemic	-26.658	6.227	-4.281	<.001
Healthy-Neuropathic	-28.367	6.957	-4.077	<.001
Healthy-Neuroischaemic	-29.700	7.295	-4.071	<.001
Ischaemic-Neuropathic	-1.708	8.209	-.208	.835
Ischaemic-Neuroischaemic	-3.042	8.497	-.358	.720
Neuropathic-Neuroischaemic	-1.333	9.046	-.147	.883

Table 4:100: Kruskal-Wallis Test (Fifth toe ROI)

Fifth MTH				
	Test Statistic	Std. Error	Std. Test Statistic	Sig.
Healthy-Ischaemic	-23.824	6.227	-3.826	<.001
Healthy-Neuroischaemic	-28.220	7.295	-3.869	<.001
Healthy-Neuropathic	-29.602	6.957	-4.255	<.001
Ischaemic-Neuroischaemic	-4.396	8.496	-.517	.605
Ischaemic-Neuropathic	-5.778	8.208	-.704	.481
Neuroischaemic-Neuropathic	1.382	9.045	.153	.879

Table 4:101: Kruskal-Wallis Test (Fifth MTH ROI)

The 0.05 level of significance was not exceeded when the cutaneous temperature of healthy feet was compared with that of participants with T2DM foot complications and therefore the null hypothesis is rejected. This confirms that there is statistically significant difference in plantar foot temperatures between participants with T2DM foot complications and healthy T2DM participants. Furthermore, the 0.05 level of significance was exceeded when the mean temperature of the foot was compared between the different types of T2DM foot complications. This shows that there are no significant differences in plantar foot temperatures between the different T2DM foot complications groups. These statistical inferences were recorded in all the ROI of the toes and forefoot.

These results confirm that statistically significantly higher plantar foot temperatures are present in participants with T2DM foot complications compared to healthy T2DM participants. No significant differences in plantar foot temperatures were recorded between the different T2DM foot complications groups. These statistical inferences were recorded in all the ROI of the toes and forefoot.

Percentage of Correct Predictions for Every T2DM Complication Group

The percentage of participants correctly predicted to have T2DM foot complications for every T2DM foot complication group was recorded. This was done separately for every ROI and for every probability cut-off point.

Toes

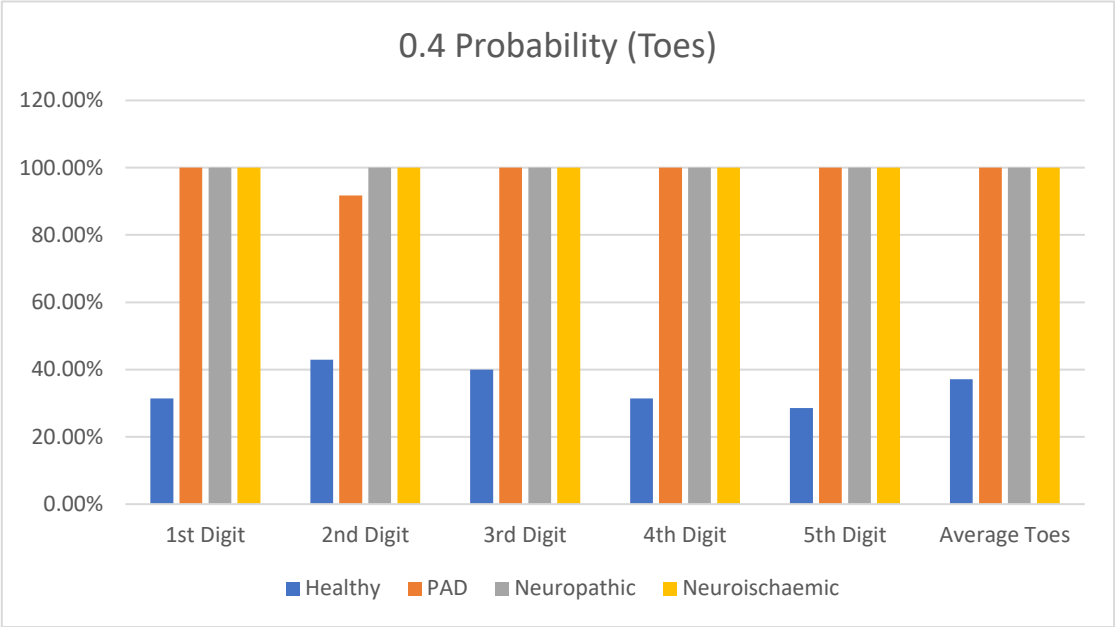

Figure 4.42: Percentage of correct predictions using 0.4 probability cut-off point (Toes).

0.4 Cut-off Point	1st Digit	2nd Digit	3rd Digit	4th Digit	5th Digit	Average Toes
Healthy	31.40%	42.90%	40%	31.40%	28.60%	37.10%
PAD	100%	91.70%	100%	100%	100%	100%
Neuropathic	100%	100%	100%	100%	100%	100%
Neuroischaemic	100%	100%	100%	100%	100%	100%

Table 4:102: Percentage of correct predictions using 0.4 probability cut-off point (Toes).

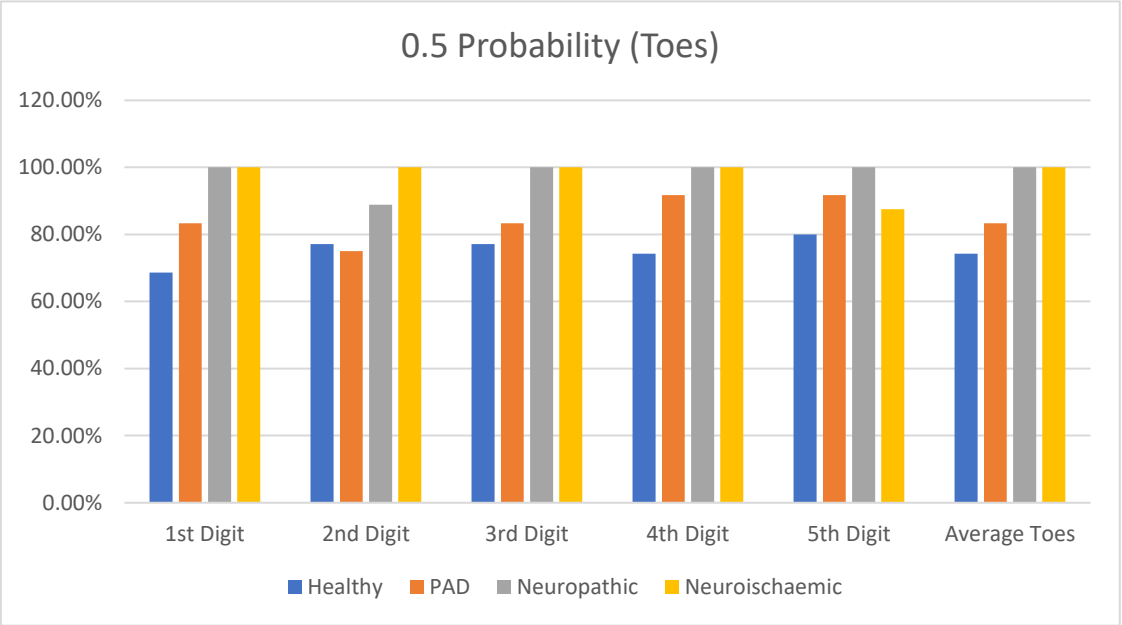

Figure 4.43: Percentage of correct predictions using 0.5 probability cut-off point (Toes).

0.5 Cut-off Point	1st Digit	2nd Digit	3rd Digit	4th Digit	5th Digit	Average Toes
Healthy	68.60%	77.10%	77.10%	74.30%	80%	74.30%
PAD	83.30%	75%	83.30%	91.70%	91.70%	83.30%
Neuropathic	100%	88.90%	100%	100%	100%	100%
Neuroischaemic	100%	100%	100%	100%	87.50%	100%

Table 4:103: Percentage of correct predictions using 0.5 probability cut-off point (Toes).

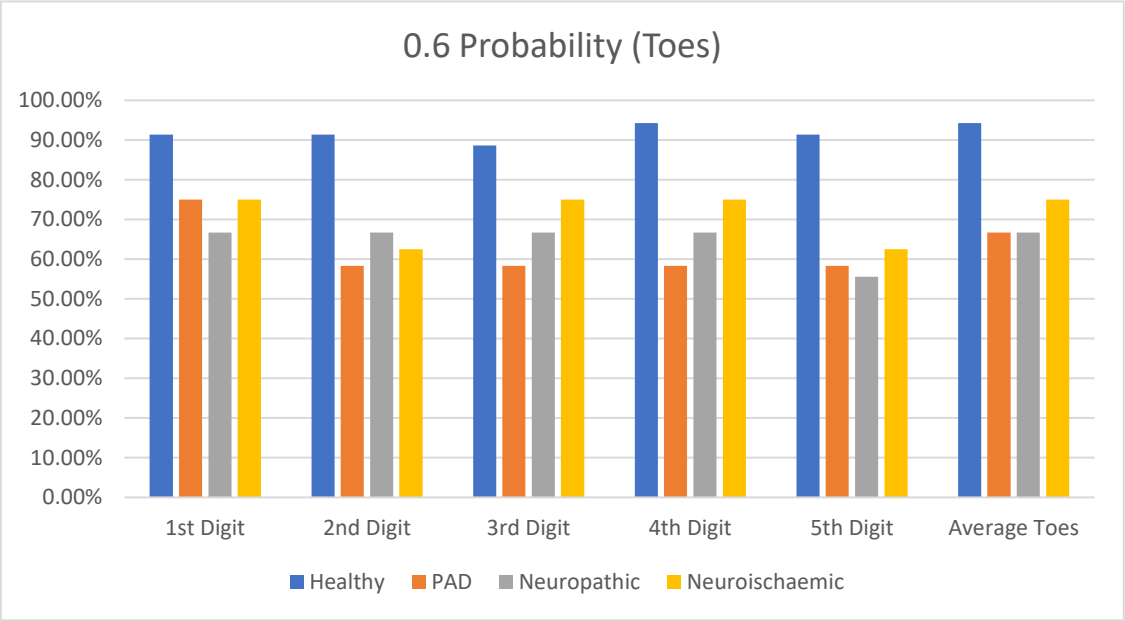

Figure 4.44: Percentage of correct predictions using 0.6 probability cut-off point (Toes).

0.6 Cut-off Point	1st Digit	2nd Digit	3rd Digit	4th Digit	5th Digit	Average Toes
Healthy	91.40%	91.40%	88.60%	94.30%	91.40%	94.30%
PAD	75%	58.30%	58.30%	58.30%	58.30%	66.70%
Neuropathic	66.70%	66.70%	66.70%	66.70%	55.60%	66.70%
Neuroischaemic	75%	62.50%	75%	75%	62.50%	75%

Table 4:104: Percentage of correct predictions using 0.6 probability cut-off point (Toes).

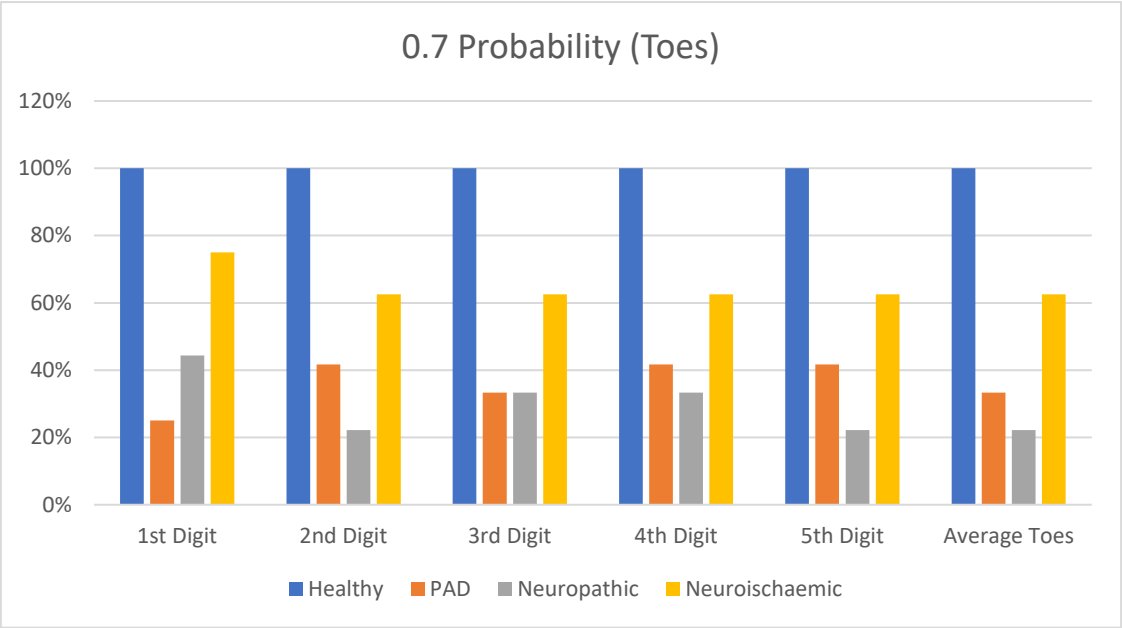

Figure 4.45: Percentage of correct predictions using 0.7 probability cut-off point (Toes).

0.7 Cut-off Point	1st Digit	2nd Digit	3rd Digit	4th Digit	5th Digit	Average Toes
Healthy	100%	100%	100%	100%	100%	100%
PAD	25%	41.70%	33.30%	41.70%	41.70%	33.30%
Neuropathic	44.40%	22.20%	33.30%	33.30%	22.20%	22.20%
Neuroischaemic	75%	62.50%	62.50%	62.50%	62.50%	62.50%

Table 4:105: Percentage of correct predictions using 0.7 probability cut-off point (Toes).

In the toes ROI, all participants with neuropathy were correctly predicted to have T2DM foot complications when using a 0.4 probability and 0.5 probability cut-off points. Nearly all participants with neuroischaemia were also identified when using toes ROIs and 0.4 and 0.5 cut-off points. The only exception being in the 5th digit ROI when using 0.5 probability cut-off point. Nearly all participants with PAD were also correctly predicted when using the 0.4 probability cut-off point in the toes ROIs with the only exception being in the 2nd digit ROI. Participants with PAD were less likely to be identified compared to the other two T2DM foot complications groups when using the 0.5 probability cut-off point.

Forefoot

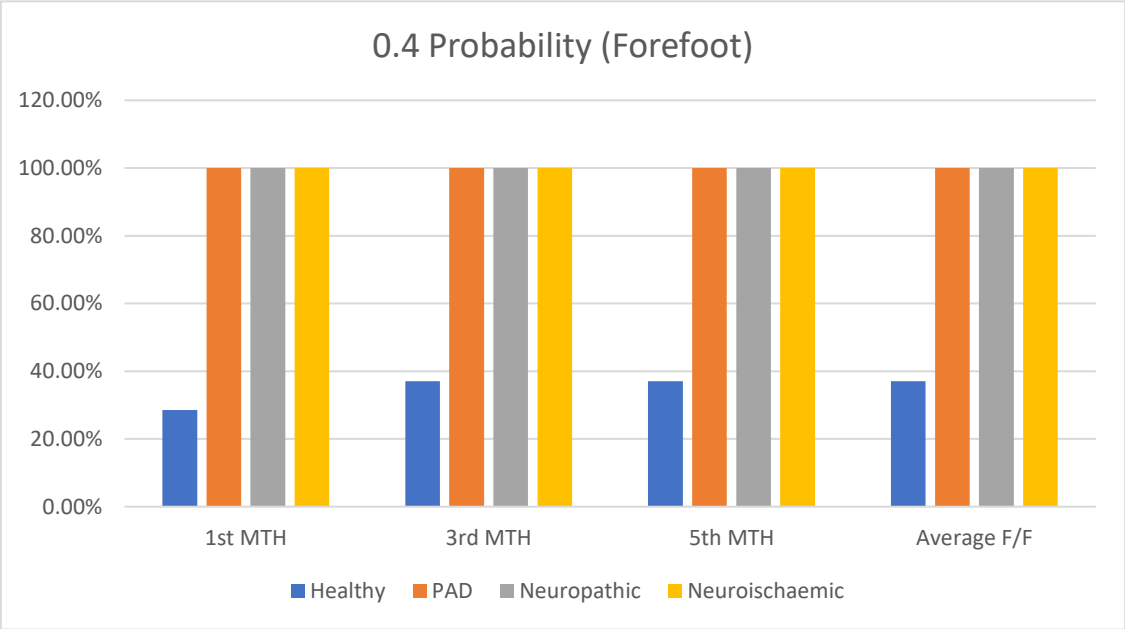

Figure 4.46: Percentage of correct predictions using 0.4 probability cut-off point (Forefoot).

0.4 Cut-off Point	1st MTH	3rd MTH	5th MTH	Average F/F
Healthy	28.50%	37.10%	37.10%	37.10%
PAD	100%	100%	100%	100%
Neuropathic	100%	100%	100%	100%
Neuroischaemic	100%	100%	100%	100%

Table 4:106: Percentage of correct predictions using 0.4 probability cut-off point (Forefoot).

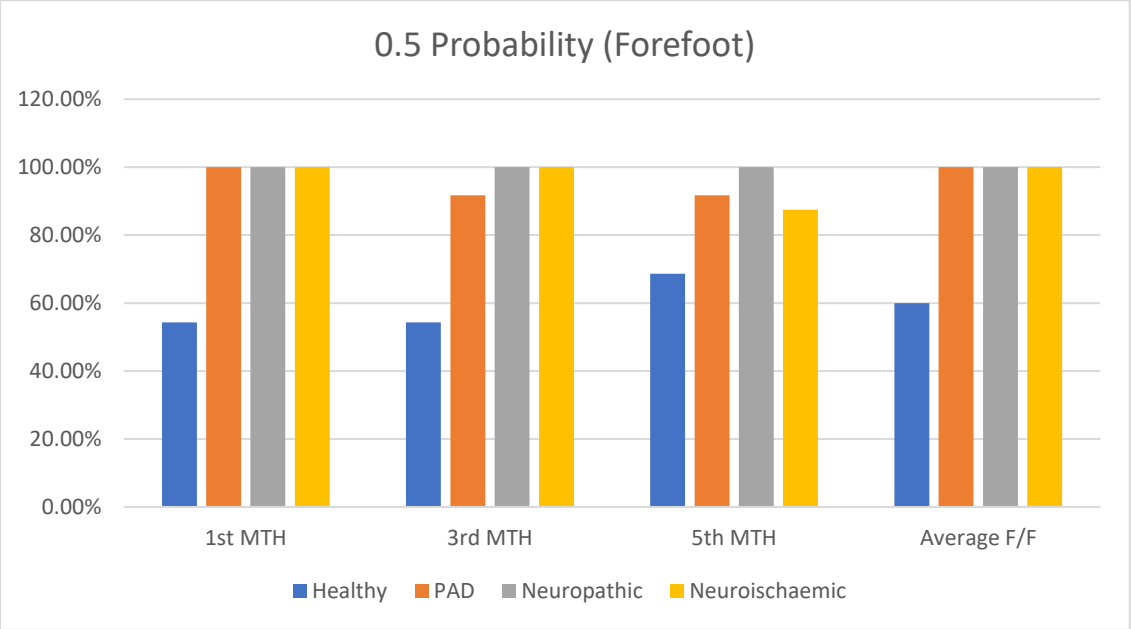

Figure 4.47: Percentage of correct predictions using 0.5 probability cut-off point (Forefoot).

0.5 Cut-off Point	1st MTH	3rd MTH	5th MTH	Average F/F
Healthy	54.30%	54.30%	68.60%	60%
PAD	100%	91.70%	91.70%	100%
Neuropathic	100%	100%	100%	100%
Neuroischaemic	100%	100%	87.50%	100%

Table 4:107: Percentage of correct predictions using 0.5 probability cut-off point (Forefoot).

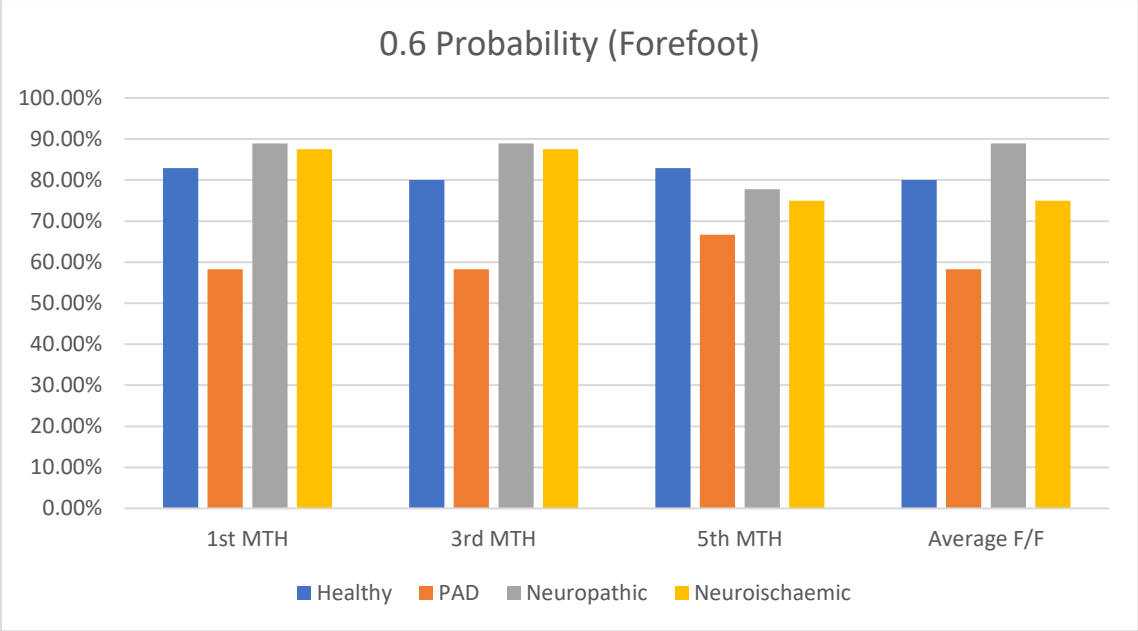

Figure 4.48: Percentage of correct predictions using 0.6 probability cut-off point (Forefoot).

0.6 Cut-off Point	1st MTH	3rd MTH	5th MTH	Average F/F
Healthy	82.90%	80%	82.90%	80%
PAD	58.30%	58.30%	66.70%	58.30%
Neuropathic	88.90%	88.90%	77.80%	88.90%
Neuroischaemic	87.50%	87.50%	75%	75%

Table 4:108: Percentage of correct predictions using 0.6 probability cut-off point (Forefoot).

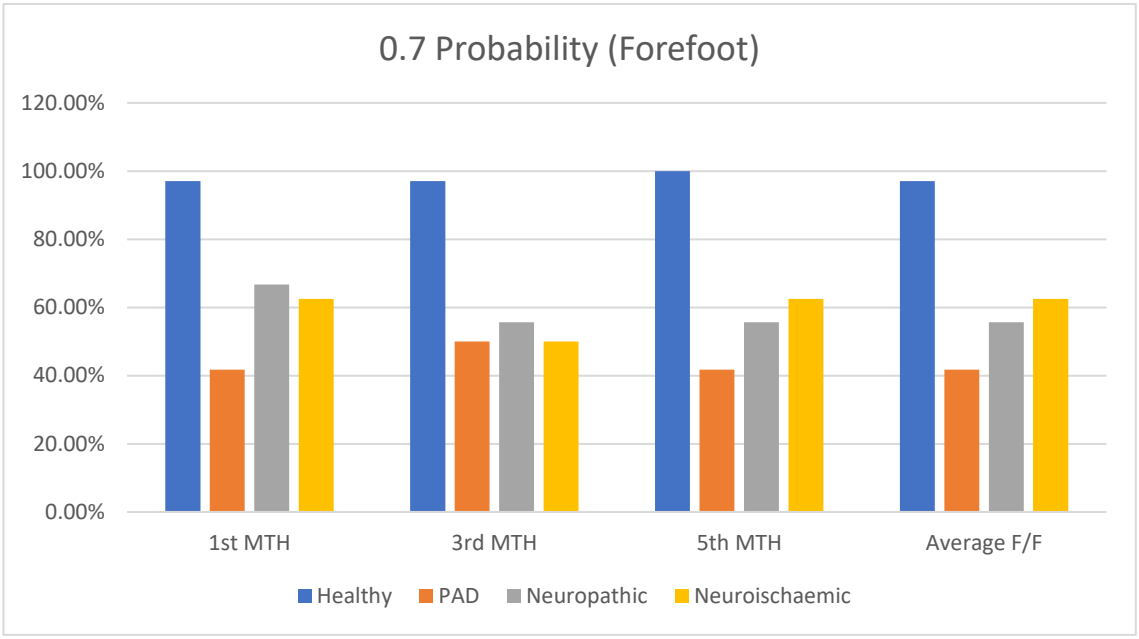

Figure 4.49: Percentage of correct predictions using 0.7 probability cut-off point (Forefoot).

0.7 Cut-off Point	1st MTH	3rd MTH	5th MTH	Average F/F
Healthy	97.10%	97.10%	100%	97.10%
PAD	41.70%	50%	41.70%	41.70%
Neuropathic	66.70%	55.60%	55.60%	55.60%
Neuroischaemic	62.50%	50%	62.50%	62.50%

Table 4:109: Percentage of correct predictions using 0.7 probability cut-off point (Forefoot).

Similar to the results obtained in toes ROI, nearly all participants with neuropathy and neuroischaemia were correctly predicted to have T2DM complications when using a 0.4 and 0.5 probability cut-off points. The only exception being in the 5th MTH ROI of participants with neuroischaemia when using a 0.5 probability cut-off point. All participants with PAD were correctly predicted when using a 0.4 probability cut-off point.

Conclusion

From the results obtained, it can be noted that sensitivity to T2DM foot complications decreased while specificity increased when the probability cut-off point was increased from 0.4 to 0.7. When using a 0.5 probability cut-off point, no false negatives were observed in the average forefoot and 1st MTH ROIs (sensitivity=1), while the specificity varied between 0.54 and 0.69. In the toes ROIs, a sensitivity between 0.93 and 0.97 and a specificity ranging between 0.69 and 0.8 were recorded when using a 0.5 probability cut-off point.

From the data collected it can be observed that with an increase in sensitivity there in a decrease in the positive predictive value and an increase in the negative predictive value in all the ROIs investigated.

Nearly all neuropathic and neuroischaemic participants were correctly identified in all the ROIs investigated when using a 0.4 and 0.5 probability cut-off point. Similarly, nearly all participants with PAD were also identified when using a 0.4 probability cut-off point, however, much less participants were identified when using a 0.5 probability cut-off point compared to the other two T2DM groups (neuropathy and neuroischaemia). Participants with PAD were more likely to be correctly predicted when using forefoot temperatures rather than toe temperatures.

These results will be discussed in detail in chapter five together with an analysis of how these findings relate to previous studies, limitations, implications of this research and recommendations for future research.

Chapter 5 : Discussion

Introduction

Studies have already linked higher foot cutaneous temperatures in patients with T2DM to the presence of neuropathy. (Papanas et al., 2009; Bagavathiappan et al., 2010; Ilo, Romsi & Mäkelä, 2019). Research regarding the foot temperature in patients with PAD is more conflicting. Some research suggests that it is associated with lower foot temperature, while some suggest that higher foot temperatures are present even in patients with PAD (Seixas et al., 2018; Carabott et al., 2018). However, research from the University of Malta has identified significantly higher foot temperatures in subjects with all types of diabetic foot complications (PAD, neuropathy, & neuroischaemia) (Gatt et al., 2018). Additionally, an increase in cutaneous temperature correlates with a higher likelihood of T2DM foot complications, while decreasing the probability of the feet being healthy and vice versa. This was supported by logistic regression curves and formulas that produce the probability of T2DM foot complications based on foot temperature. With 10.1% of the Maltese population living with T2DM, there is a significant burden on clinicians to conduct diabetic foot screenings annually, as advised by the American Diabetic Association (2018). Therefore, it's worth considering whether thermography can effectively detect these complications and serve as a dependable and efficient screening method.

This study aimed to determine whether thermography can be used as a screening tool to identify T2DM foot complications. This involved capturing a thermogram of the foot and dividing it into eight ROIs. The mean temperature for each ROI was recorded, and the probability of foot complications was calculated using formulas retrieved from the study of Gatt et al. (2018). Several probability cut-off points (0.4, 0.5, 0.6 and 0.7) were used to predict whether T2DM foot complications were present. Medically validated tests consisting of ABPI, doppler, 10g monofilament and 128Hz tuning fork were carried out by another podiatrist to ensure blindness and eliminate bias. The prediction was later compared to the actual presence or exclusion of T2DM foot complications and the sensitivity, specificity, NPV and PPV were recorded. Furthermore, one-way ANOVA with a post-hoc Tukey test was done, which confirmed a significant difference in cutaneous temperatures of the foot between subjects with T2DM foot complications and subjects without complications.

Analysis of Results

From the statistical analysis in chapter four, one can note that in all the ROIs, there were significantly higher cutaneous temperatures in the participants with T2DM foot complications compared to healthy participants. There were no significant differences in cutaneous temperatures between the different T2DM foot complications (neuropathy, PAD, and neuroischaemia) in all the ROIs. The mean forefoot cutaneous temperatures in participants with PAD, neuropathy, and neuroischaemia were found to be 30.01^{o}C, 30.83^{o}C, and 30.89^{o}C respectively. In participants without foot complications, the mean forefoot temperature was 26.78^{o}C. Similarly, in the toes, the mean cutaneous temperatures of participants with PAD, neuropathy, and neuroischaemia were 29.23^{o}C, 29.26^{o}C and 30.44^{o}C, while that of participants with no complications was 25.06^{o}C. Gatt et al. (2015) also found that individuals with T2DM consistently exhibit higher temperatures in their forefoot compared to their toes. Although the temperature of the toes is typically lower than that of the forefoot, separate equations were used to predict the risk of complications for these regions.

To determine if thermography can be used to identify T2DM complications, the sensitivity, specificity, NPV and PPV of each ROI were calculated. As the results obtained in this research shows, this method has produced very high sensitivity in detecting T2DM foot complications in all the ROIs investigated when using 0.4 and 0.5 probability cut-off points. When using a 0.5 probability cut-off point, sensitivity was found to be between 93% to 97% in the toes and between 93% and 100% in the forefoot. This means that nearly all participants diagnosed with T2DM foot complications were correctly predicted to have these complications when using a 0.5 probability cut-off point. Very high specificity can be observed in all the ROIs investigated using 0.6 and 0.7 probability cut-off points. When using a 0.5 probability cut-off point, the specificity was found to be between 54% and 69% in the forefoot. In the toes, specificity ranged from 69% to 80%.

When utilising this method to detect T2DM complications, it is observed that there is a higher sensitivity but lower specificity. This indicates that false positive results are more likely than false negatives. The outcomes reveal that the sensitivity and specificity of all the ROIs investigated are comparable, indicating that any area on the forefoot and toes can be utilized for evaluation.

This data shows that with an increase in the probability cut-off point, there is a decrease in sensitivity and an increase in specificity. This is because when the probability cut-off point is increased to 0.7, participants with a 0.6 chance of having T2DM foot complications were considered healthy. Therefore, the number of false negative results increases. On the other hand, when decreasing the probability cut-off point to 0.4, participants with a 0.45 probability were considered to have T2DM foot complications. Therefore, this increases false positive results. A major limitation of sensitivity and specificity is that since these values are based on people with or without the disease, it doesn`t provide the clinician with the probability of the test result being accurate (Habib Hanga et al., 2015). That is why the NPV and PPV were also calculated. NPV refers to the probability that a negative test is accurate, while PPV refers to the probability that a positive test is accurate. When using a 0.5 probability cut-off point, the PPV varied from 0.71 to 0.79 in the toes and from 0.64 to 0.71 in the forefoot. The NPV values ranged from 0.92 to 0.96 in the toes and from 0.92 to 1 in the forefoot. With an increase in the probability cut-off point, there was an increase PPV value and a decrease in the NPV value.

A 0.5 probability cut-off point is most effective as it generates well-balanced sensitivity, specificity, NPV, and PPV values. This cut-off point offers an exceptionally high level of sensitivity, resulting in fewer false negative results and precise identification of participants suffering from foot complications caused by T2DM. High sensitivity is a crucial aspect of screening because it allows for the identification of most cases of T2DM foot complications, ensuring that very few are missed. Additionally, the high level of specificity recorded is also significant in screening, as it helps to minimize the number of false positive cases, ultimately avoiding unnecessary referrals for further testing. Furthermore, the high PPV and NPV values suggest that predicting T2DM foot complications using thermography is highly accurate.

If the 0.4 probability cut-off point is used, the sensitivity increases, but the specificity decreases compared to using the 0.5 probability cut-off point. This may result in an elevated number of false positive outcomes, indicating that a substantial number of healthy T2DM patients may be identified as having T2DM foot complications. Consequently, an excessive number of patients may be referred for vascular and neurological testing if the 0.4 cut-off point is used for screening. If the 0.6 and 0.7 probability cut-off points are used, the sensitivity decreases, resulting in more false negative results. Using these cut-off points may result in overlooking more patients with T2DM foot complications compared to using the 0.5 and 0.4 probability cut-off points. This is not ideal for screening purposes.

Furthermore, the percentage of correctly predicted outcomes (sensitivity) for every type of T2DM foot complication was also analysed. These results showed that with a 0.5 probability cut-off point, all participants with neuropathy, PAD and neuroischaemia were correctly predicted to have T2DM foot complications when using the 1st MTH ROI. From the results obtained, it can be observed that with an increase in probability cut-off point, there is a decrease in the percentage of correct predictions in all three T2DM foot complication groups.

Interpretation of Results

Diabetic Foot Complications and Foot Temperatures

Despite numerous studies on the application of thermography in diabetic foot monitoring, only a limited number of studies have examined the accuracy of thermal cameras in detecting chronic complications of T2DM in the foot. The majority of existing research primarily concentrates on the sudden increase in skin temperature preceding ulceration.

An acute increase in cutaneous temperature can be an early sign of pre-ulceration inflammation (Lavery et al., 2007; Armstrong et al., 2007). Several studies have confirmed this increase in cutaneous temperature before an ulcer develops (Sun et al., 2005; Houghton, Bower & Chant, 2013; Benbow et al., 1994; Yavuz et al., 2019). The study's findings suggest that elevated skin temperatures may result not only from an imminent ulcer but also from chronic conditions such as peripheral neuropathy, PAD, or neuroischemia.

The findings validate the results of a previous study conducted by Gatt et al. (2018), which revealed substantially elevated temperatures in the plantar foot region of T2DM patients with neuropathy, ischaemia, or neuroischaemia as opposed to those without foot complications. Additionally, the study conducted by Carabott et al. (2018) also supports the notion of increased temperatures in individuals with PAD, which has been a topic of debate in the past. Ilo et al. (2020) also agree with Gatt et al. (2018), reporting that there was an increase in foot temperature in the presence of neuropathy. Neuroischemic and ischemic feet were also found to be warmer than healthy feet.

Several studies have suggested using thermogram-based methods to analyse the diabetic foot. These studies reported a distinct butterfly pattern in control groups, while patients with diabetes displayed a wide range of spatial patterns (Nagase et al., 2011). Research suggests that comparing the thermal characteristics of one foot with the other as a reference can be a useful technique. However, this method may not be effective if both feet experience temperature changes or if the patient has undergone amputation.

The difference in foot temperature between opposite feet of patients with diabetes was reported by Van Netten et al. (2014). A temperature difference of 2.2ºC between contralateral spots can detect diabetes-related foot complications. The authors reported a sensitivity of 76% and a specificity of 40%. A temperature difference of 1.35ºC between the left and right feet was considered the optimal cut-off temperature to determine the urgency of treatment. This had a sensitivity of 89% and a specificity of 76%. The results of Van Netten et al. (2014) study indicate high sensitivity and specificity. However, contrary to the method used in this research, it is not applicable to patients with lower limb amputations since it relies on comparing the limbs on both sides. Ilo et al. (2020) also identified greater side-to-side temperature differences between the feet of patients with diabetes healthy subjects. The difference was between 0ºC and 10.2ºC in patients with diabetes and between 0ºC and 3.1ºC in the healthy control group.

Another system which may be able to differentiate between 3 different types of diabetic complications (neuropathy, ischaemia, and neuroischaemia) and healthy diabetics was proposed by Eid et al. (2018). The researchers proposed a system based on amalgamating textural and histogram features of foot thermograms. These were then classified using three different classifiers: (i) k-Nearest Neighbor (kNN); (ii) Support vector machine, and Decision tree. This proposed design provided short time analysis and accurate automatic classification of the diabetic foot using a thermogram. Based on the analysis, it was determined that the kNN method yielded the most favourable outcomes, with a precision rate of 96.8%, a sensitivity rate of 88.3%, and a specificity rate of 99.1%.

The ability of the CNN (Convolutional Neural Network) software to distinguish between four groups of subjects with diabetic complications and healthy non-diabetic subjects by using thermograms of the plantar aspect of the foot was studied by Muralidhara et al. (2022). The researchers compared accuracy with other traditional tests and other software. The Thermal Change Index was used as an indicator to analyse each ROI separately and independently. Its

thermal data were then compared to control data and automatically analysed through the CNN software. Comprehensive data on each ROI and any possible limitations related to contralateral thermal comparison as well as relative temperature comparison are provided. The probability of the presence of diabetic complications is increased with an increase in the Thermal Change Index. This software has produced an accuracy of 98.2% and a sensitivity of 96.8%. This demonstrates the usefulness and reliability of such software techniques.

Eid et al. (2018) and Muralidhara et al. (2022) provide further evidence that with the use of specialised automated software programs, there can be an improved extraction of mean temperature data compared to manual techniques in both time efficiency and accuracy. This suggests that if a specialised automated software can be developed utilising the method used in this study, the sensitivity and specificity can be increased even more.

Neuropathy and Foot Temperature

Contrary to Boyko et al. (2001), who reported lower foot temperatures in diabetic patients with peripheral sensory neuropathy than without neuropathy, this study showed a higher mean temperature in patients with peripheral neuropathy compared to healthy participants. A reason for this could be the difference in diagnostic criteria for diagnosing participants with peripheral neuropathy. Boyko et al. (2001) defined sensory neuropathy as any pedal insensitivity to the 10g monofilament in any site of the foot, whereas, in this research, both 10g monofilament and 128Hz tuning fork were used for diagnosis.

The findings of this research align with previous studies that have shown elevated foot temperatures in individuals with neuropathy (Bagavathiappan et al., 2010; Papanas et al., 2008; Gatt et al., 2018). This study accurately identified all participants with neuropathy in all the ROIs investigated, except for the 2nd digit ROI, when using a cut-off point of 0.5 probability. The study revealed that individuals with peripheral neuropathy had comparable cutaneous temperatures to those found in the study conducted by Yavuz et al. (2019), who recorded mean toe temperatures of 30.7°C and central metatarsal temperatures of 31.7°C in patients with diabetic peripheral neuropathy.

Papanas et al. (2008) not only found higher foot temperatures in neuropathic patients, but they also found that with an increase in the severity of neuropathy, there is an increase in foot temperature based on data acquired using infrared thermography. Diabetic Neuropathy Index (DNI) was used by Papanas et al. (2008) when diagnosing neuropathy. DNI is a standard test applied to each foot independently, which examines appearance, neuropathic ulceration, ankle reflexes and vibration perception at the hallux. A DNI score higher than two was used to diagnose neuropathy. The authors attribute this increase in temperature with the increase in neuropathy severity to greater disruption of the neurogenic control of small blood vessels causing more blood flow to the foot, therefore causing an increase in cutaneous temperature.

Foot skin temperature ≥ 32°C was found to have a moderately high sensitivity and specificity for diagnosing neuropathy, as Papanas et al. (2008) reported. The plantar aspect of the foot had a 63.3% sensitivity and 100% specificity, while the dorsal aspect of the foot had a 76.7% sensitivity and 80% specificity. The method utilized in this research was highly effective in identifying peripheral neuropathy, as all participants with the condition were successfully detected. Additionally, the study demonstrated greater sensitivity not only in detecting neuropathy but also in detecting all three types of foot complications associated with T2DM compared to Papanas et al.'s (2008) research.

No direct correlation between HbA1c and mean foot temperature or diabetic neuropathy was found by Bagavathiappan et al. (2010). Apart from higher temperatures in patients with neuropathy, Ilo et al. (2019) also reported higher foot temperatures in patients with neuroischaemia. The studies cited previously established a link between elevated temperatures and neuropathy.

These findings can be attributed to the thermoregulatory mechanisms of the feet. Diabetes is associated with a great deal of functional abnormalities of the microvasculature. A chronic increase in cutaneous temperatures in patients with diabetic peripheral neuropathy has been attributed to an increase in arteriovenous shunt flow (Nagase et al., 2011). Arteriovenous anastomoses are low-resistance conduits that allow blood to flow directly from arterioles to venules richly innervated by sympathetic vasoconstrictor nerves.

Peripheral Arterial Disease and Foot Temperature

When it comes to identifying PAD in patients with T2DM, different screening modalities give different results. Midolo Azzopardi et al. (2018) found a large degree of inconsistency between different modalities in detecting PAD. When using the Doppler waveform, 93% of participants were found to have PAD, compared to 72% when using TBPI, 57% when using ABPI, and 23% when using pulse palpation. Approximately one-third of patients with diabetes have arterial sclerosis that renders arteries incompressible by cuff inflation which may cause falsely elevated values when using ABPI. This shows that some commonly used tests are not very sensitive in detecting PAD. This research shows that thermography can be very sensitive in identifying T2DM foot complications, including PAD. When faced with uncertain cases, infrared thermography may be utilized alongside other screening methods to offer supplementary information that can aid in the decision-making process towards a clear diagnosis.

There is no agreement in research regarding the effect of PAD on foot temperature. Hayashi & Shichiri (2020) found lower foot skin temperatures in patients with PAD than those without. The authors stated that a temperature less than 30.8ºC in any of the three ROIs (1st MTH, 3rd MTH or heel) have an increased risk of having PAD and would require more medical tests. Furthermore, they reported that when using a cut-off point of the lowest skin temperature <30.8ºC, it produces a sensitivity of 60% and specificity of 64%. The results of this research contradict the findings of Shichiri (2020) and support the conclusions of Gatt et al. (2018) and Carabott et al. (2018) that individuals with T2DM and PAD exhibit higher plantar foot temperatures. One possible explanation for the disparity in findings could be attributed to the fact that Hayashi & Shichiri (2020) employed Thermofocus (01500A3; Technimed, Varese, Italy) to gauge cutaneous temperature, whereas a more advanced FLIR thermal camera was utilized in this research. Furthermore, the method used in this research had much higher sensitivity to detecting PAD compared to the study of Shichiri (2020).

Gatt et al. (2018) stated that the probability that the participant has T2DM foot complications is raised by 28.9% for every 1°C increase in plantar forefoot temperature and 24.7% for every 1°C increase in the temperature of the toes. It is crucial to utilize accurate and dependable tools while measuring cutaneous temperatures, as even a small change of 1 degree Celsius can

substantially increase the likelihood of T2DM complications. This emphasizes the significance of precision in temperature measurement to predict outcomes accurately.

Carabott et al. (2019) have described an increase in cutaneous temperatures in patients with PAD compared to healthy diabetic patients. Schmidt et al. (2020) found that smoking status and pack-year history were associated with higher rearfoot temperatures. This increase in temperature was not found in other areas of the foot, contrary to results from this research which found higher cutaneous temperature in the forefoot and toes. Schmidt et al. (2020) attribute these rearfoot temperature changes to smoking-induced endothelial dysfunction, lipoprotein metabolism, coagulation, and platelet function leading to the calcification of blood vessels.

A different method was studied by Deus Passos and da Rocha (2022). In their study, a thermogram showing a difference in temperature greater than 2.00°C between any two points on the lower limb (including the feet) or between both was considered a sign that PAD is present. The diagnosis of PAD was made using colour Doppler ultrasonography. This infrared thermography-based procedure to detect PAD resulted in 97.62% sensitivity and 91.67% specificity; however, this diagnostic method was found to be limited in identifying supra popliteal PAD, which manifests above the knees.

For this study, the FLIR Research IR software was utilised to determine the average temperature of each ROI by manual demarcation. Various researchers utilize varying techniques to extract temperature data from foot thermograms. While manual demarcation of ROIs is a prevalent approach in research, more sophisticated software is being developed to offer a more precise and streamlined method of obtaining temperature readings. Automatic extraction of data from several ROIs through MATLAB program and how it compares to manual delimitation data extraction in diabetic patients with PAD was studied by Gauci et al. (2018). The researchers reported a correct extraction in around 90% of the images. Moreover, the automatic extraction of 44 ROIs in the hands, feet, and shins took around 1 minute compared to 10 minutes for manual extraction by a trained individual. The researchers concluded that although there was no significant increase in accuracy when using automated processes, it can be significantly less time-consuming.

In patients with PAD, the increase in cutaneous temperature is thought to be brought about by disruption of noradrenergic vasoconstrictor thermoregulatory mechanisms. This causes the

blood to flow through cutaneous vessels rather than deeper nutritive vessels leading to increased heat emissivity (Gatt et al., 2018; Ilo et al., 2020).

Implications of the Research and Practical Applications

Patients with T2DM complications are associated with warmer feet. This research confirms that increased foot temperature is an indicator for all types of diabetic foot complications; however, large-scale prospective studies are needed to validate these results. Given the high sensitivity and specificity for predicting these complications that were acquired using equations from the study of Gatt et al. (2018), it could be argued that thermography can function as a screening tool for identifying T2DM-related complications.

This research has two significant implications: First, it can help reduce the waiting time of patients with T2DM waiting for diabetic foot screening. Second, it can aid in the prompt detection of T2DM foot complications.

Reducing Wait Time for Diabetic Foot Screening.

Screening for diabetic peripheral neuropathy and PAD can be complex and time-consuming, using tools such as ABPI, doppler, 10g monofilament, and 128Hz tuning fork. In fact, an ABPI assessment alone takes around 15 minutes (McClary & Massey, 2023). According to the American Diabetes Association (2018), it is advisable for people with diabetes to receive a comprehensive foot examination every year. However, this can result in a backlog of patients waiting for diabetic foot screening, and increase pressure on healthcare professionals to complete the screenings promptly. Time constraints have been identified as the most common obstacle in conducting vascular assessments (Tehan et al., 2019). Furthermore, in many healthcare systems, the monetary value and time spent delivering healthcare services are significant factors (Abu-Qamar, 2006).

Although many studies have shown the advantages of temperature assessment, it still isn't commonly used in clinical settings. Fortunately, healthcare professionals could benefit from using thermal cameras to identify diabetic foot complications. The research suggests that thermography can be used as a screening process to detect diabetic foot issues early on. This could help with improved management and prevention of unwanted complications.

This method could reduce the number of patients requiring medically validated tests for clinical screening. If thermography were to be used in clinical settings, those with a high likelihood of T2DM foot complications could be referred for further investigation, such as Doppler, ABPI, or monofilament testing, to confirm or rule out the presence of complications. With a 0.5 probability cut-off point, this method has high PPV and NPV values, allowing clinicians to predict the presence of T2DM foot complications confidently. This would alleviate the burden on diabetic foot screening departments, as a simple thermogram of the plantar aspect of the foot would suffice.

The thermal camera is more than just an additional tool for podiatrists. It can be utilized for mass screening of diabetic patients as it saves time, doesn't require physical contact, and is a safe way to identify those at risk. This research may aid in developing infrared thermography software that automatically detects skin temperature abnormalities in patients with T2DM.

Early Detection of T2DM Foot Complications

By utilizing thermography to reduce the waiting time for diabetic foot screening, it is possible to conduct sooner foot examinations that could detect T2DM foot complications at an earlier stage. It's crucial to detect and treat diabetes-related foot complications, such as PAD, neuropathy, and neuroischemia, early on to prevent the severe consequences that come with these issues, including high morbidity and mortality rates (Bakker et al., 2011; Boulton et al., 2005). According to a study by Chaudhary et al. (2021), over half of diabetic patients with a foot ulcer infection underwent some form of amputation. However, receiving podiatric care within a year before the ulcer's development can significantly reduce the risk of amputation and hospitalisation (Gibson et al., 2014). Given the increasing number of minor amputations

due to diabetic foot complications in Malta, there is a pressing need to identify high-risk feet and provide the appropriate care (Schembri et al.,2022).

Research shows that monitoring the temperature of the soles of the feet could potentially reduce the risk of developing ulcers. According to a study by Lavery et al. (2004), checking foot temperature every day can significantly reduce the chances of developing ulcers and needing amputation. The study revealed that only 2% of diabetic patients who monitored their foot temperature daily experienced complications, compared to 20% of diabetic patients who did not monitor their foot temperature regularly. The decrease in risk of ulcer development through regular home monitoring of foot temperature was also confirmed by Armstrong et al. (2007). According to their study, patients who eventually developed an ulcer experienced a temperature difference that was 4.8 times higher at the ulcer site during the week prior to the ulcer's appearance, compared to those who did not develop an ulcer. Participants in the group with home temperature monitoring were associated with a significantly longer time for an ulcer to develop.

In a similar study by Skafjeld et al. (2015), subjects were randomly allocated to either the standard therapy group or the intervention group. Subjects in the intervention group were instructed to measure the temperature on each foot daily and record the temperature measurements. The standard therapy group were instructed to record daily foot inspection observations. 50% of subjects in the control group developed an ulcer (n=10) compared to 39% of subjects in the intervention group (n=7). While there were fewer cases of ulcers in the intervention group, this difference was not statistically significant compared to the control group (p=0.407).

Multiple clinical practice guidelines have recommended remote temperature monitoring, including the International Working Group on the Diabetic Foot, the American College of Foot and Ankle Surgeons, and the Wound Healing Society (Rothenberg et al., 2020). Individuals can benefit from the accessibility and cost-effectiveness of small mobile thermal cameras, making them a valuable tool for home temperature monitoring.

Most home temperature monitoring research involves the acute rise in temperatures presiding an ulcer (Lavery et al., 2004; Armstrong et al., 2007; Skafjeld et al., 2015). The approach utilized in this study is well-suited for at-home monitoring because it has the ability to predict chronic T2DM foot complications with great accuracy at an earlier stage. In addition, this

method does not require comparing temperatures with the other foot, making it a suitable option for diabetic patients who have undergone amputations. However, more research is needed to determine if smaller and more affordable thermal cameras or even other temperature measurement technologies that patients at home can use are as reliable as more advanced thermal cameras such as the one used in this study.

Limitations

Weaknesses in research design could affect the results and conclusions of the study; therefore, it is imperative that researchers present a complete and honest account of possible limitations present (Ross & Zaidi, 2019). When analysing the study's limitations, the researcher should not only list the potential limitations but also explain their implications, provide possible alternatives, and state the action taken to minimize the effect of these limitations.

Limitations can occur throughout all the stages of the research process. Starting from the data collection, possible limitations may include the Hawthorne effect, where participants alter their behaviour due to the awareness of being observed, thus affecting the data collected. In this study, this limitation was not possible since all the data collected did not depend on the behaviour of the participant.

Observer bias, also known as experimenter bias, is a type of experimental bias that occurs when the researcher's expectations or beliefs influence the interpretation of the results. The observer may unconsciously look for or interpret data in a way that confirms their expectations, leading to inaccurate or biased results. Certain characteristics of the participants could leave a favourable or unfavourable effect on the researcher leading to bias. This is also known as the Halo or Horns effect. To prevent bias based on the data from the thermal image produced, the researcher was blinded to the diagnosis of the participant and another podiatrist was tasked with performing medically validated tests.

During data analysis, limitations may occur due to the type of statistical analysis used. When researchers use convenience sampling, there is a possibility that they may not adhere to the fundamental principles of inferential statistical analysis as closely as when they use random

sampling. Having chosen convenient sampling as the method to recruit participants in this study gave space for certain limitations. Since participants were not chosen through random selection, the sample could not be fully representative of the population hence making it more difficult to generalize on the total population. The accuracy of data collected may be affected since participants were recruited based on who was available and easily accessible, thus leaving out many potential participants.

When the foot's cutaneous temperature was analysed using FlirIR software, polygons were placed manually on the selected areas. This could have given way to human error because although great attention was given to placing the polygons as accurately as possible, some variations between participants could still occur. This was due to variations in the shape and placement of the foot from one participant to another.

Limitations concerning the results of the study are tied to the validity of results which could lead to threats to the internal and external validity of the research (Price & Murnan, 2004). Effects of events external to the study may give rise to threats to the internal validity of the study. This research was carried out in the middle of the Covid-19 pandemic. Since this research involved participants that were considered as high risk for complications if they contracted the virus, most of the eligible T2DM patients refused the invitation to participate in this study. This may have led to the sample size in this study (n=64) being too small to generalize about the population. To try to overcome this problem, a longer data collection period was done. A sample size that is too small may not provide enough statistical power to detect meaningful differences or relationships in the data. Conversely, a sample size that is too large may be impractical or unnecessary, leading to a waste of resources.

Threats to the study's external validity occur when a study's results cannot be generalized to its larger population (Creswell, 2003). Therefore, it is important that the limitations of the study are identified and reported so that readers are informed about any potential hidden biases that could inhibit the generalizability of results (Ross & Zaidi, 2019).

Another limitation could be that the average age in this research was quite high. This is a limitation because of the presence of age-related health conditions and other factors that could influence the cutaneous temperature of the foot. To minimise this effect, strict inclusion/exclusion criteria were created in which possible participants with any other conditions known to influence foot temperature were not allowed to participate.

Recommendations for Future Research

This study has produced promising results when it comes to detecting diabetic foot complications. The very high sensitivity of this method makes it an ideal screening test since false negative results are rare. For this to be feasible for the podiatrist, more research is needed on whether more affordable and smaller thermal cameras produce the same results as more high-quality and expensive cameras.

From previously mentioned studies, it was seen that home temperature monitoring is an effective way to prevent further diabetic foot complications such as ulcerations. However, these studies investigated the acute rise in temperature before an ulcer develops. More research is needed to determine if this method could be useful for home temperature monitoring to detect ischaemia, neuropathy or neuroischaemia.

If this method is to be implemented for home monitoring, more studies are needed to determine the effect of ambient temperature on the cutaneous temperature of the foot as this could lead to inaccurate results.

Due to the small sample size due to external factors, the same study could be recreated but on a larger scale to generalize on the total population.

Development of an automated software that could identify the ROIs automatically. This would prevent inconsistencies from human error when these ROIs are drawn manually.

These results can be helpful in developing a specialised automated infrared thermography software that can automatically identify T2DM foot complications by recognising skin temperature abnormalities.

This study demonstrated the potential effectiveness of temperature monitoring in predicting and preventing diabetic foot complications. However, further research is needed to determine the most effective temperature methods and to identify the patients who will benefit the most from this technology.

Chapter 6 : Conclusion

An increase in cutaneous temperature due to diabetic foot complications have been reported in literature (Gatt et al., 2018; Bagavathiappan et al., 2010; Papanas et al., 2008; Carabott et al., 2019). Gatt et al. (2018) developed logistic regression curves describing an increase in the probability of T2DM foot complications with an increase in plantar cutaneous temperature. Furthermore, equations were developed that calculate the probability of these complications based on the temperature of the foot.

This research had the aim to determine whether thermography can be used as a screening modality to detect T2DM complications by measuring the cutaneous temperature of specific areas of the foot. Thermograms of the plantar aspect of the foot were captured and the mean temperature in eight ROIs was extracted. Equations from Gatt et al.'s (2018) study were employed to calculate the likelihood of complications for each ROI. Medically validated tests were conducted to diagnose or rule out T2DM foot complications. The probability of T2DM foot complications was subsequently compared to the actual presence or absence of such complications. For each probability cut-off point examined (0.4, 0.5, 0.6, 0.7), the sensitivity, specificity, PPV, and NPV were computed.

According to this research, the findings align with Gatt et al.'s (2018) study, showing that individuals with T2DM foot complications have higher temperatures compared to those with healthy feet. This research stands out because it not only acknowledges the correlations between higher temperature and T2DM foot complications (Papanas et al, 2008; Bagavathiappan et al., 2010; Gatt et al, 2018; Carabott et al., 2018) but it takes it a step further by putting this to test and prospectively predicting the likelihood of T2DM foot complications based on foot temperature.

The study reveals that raising the probability cut-off point leads to enhanced specificity and positive predictive value (PPV) but decreased sensitivity and negative predictive value (NPV). This implies that lowering the probability cut-off point boosts sensitivity but lowers the accuracy of positive test results. On the other hand, while increasing the probability cut-off point results in high specificity, it also lowers the accuracy of negative test results.

The 0.5 probability cut-off point is recommended as it generates balanced sensitivity, specificity, NPV and PPV values. This probability cut-off point provides a very high sensitivity level, resulting in fewer false negative results and precise identification of participants with T2DM foot complications. High sensitivity is a crucial aspect of screening, as it enables the identification of almost all cases of T2DM foot complications and ensures that very few are missed. The high level of specificity recorded is also an important factor in screening, as it helps minimize the number of false positive cases. This, in turn, prevents unnecessary referrals for further testing. The results from this research also showed that individuals with neuropathy, PAD, and neuroischemia were all identified as having T2DM foot complications using the 1st MTH ROI and a 0.5 probability cut-off point. In addition, the high PPV and NPV values suggest that predicting T2DM foot complications using thermography is highly accurate.

Using conservative methods to screen for foot complications related to T2DM can be a time-consuming process. In fact, the ABPI procedure alone typically takes around 15 minutes (McClary & Massey, 2023). When utilised in a clinical setting, this method can potentially decrease the wait time for foot screening of patients with T2DM. Reducing the waiting time for detection can enable early identification of T2DM foot complications. Earlier detection of T2DM foot complications can also be done if this approach is used for home temperature monitoring. Unlike other studies (Lavery et al., 2004, Armstrong et al., 2007) that focused on monitoring home temperature during sudden temperature spikes before the appearance of an ulcer, this approach can detect persistent elevation in foot temperature caused by T2DM foot complications.

According to this study, thermography can be an effective method to screen for foot complications in patients with T2DM. Thanks to technological improvements, thermal cameras have become smaller and more affordable, making them accessible to clinicians and patients alike. However, further research is required to determine if low-cost thermal cameras are as accurate as more expensive models, like the one used in this study. Moreover, combining the study's findings with artificial intelligence could improve the results even further, resulting in a faster and more precise way to detect T2DM foot complications.

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Appendices

Appendix 1: Email from FREC approving this study.

L-Università ta' Malta

Matthew Carabott <matthew.carabott.13@um.edu.mt>

UREC FORM V_11022020 5098 Matthew Carabott

Research Ethics HEALTHSCI <research-ethics.healthsci@um.edu.mt> 21 October 2020 at 13:41
To: Matthew Carabott <matthew.carabott.13@um.edu.mt>
Cc: Alfred Gatt <alfred.gatt@um.edu.mt>, Rosienne Farrugia <rosienne.farrugia@um.edu.mt>

Dear Matthew,

Further to my previous email, please note that UREC-DP has reviewed your application. Approval is granted **on condition** that the following issues are addressed by the researcher and verified by the FREC before the research commences:

1. REDP Form
1.1 The applicant ticked the 'unpublished secondary data from human participants' box on the self-assessment form but only seems to be describing primary data collection in the documents supplied. There is no mention of secondary data in the research description provided on the form itself and there is no separate detailed research proposal. It is therefore not clear if this was simply ticked in error or if there is a related aspect of the research project involving secondary data. The researcher is required to clarify this and, if unpublished secondary data is to be processed, this aspect of the study needs to be reviewed by the FREC (and by UREC-DP if SCPD are involved) before the study commences.

2. Informed Consent Form / Information Sheet
2.1 The researcher should give the participants information about any risks associated with the study. This information must be explicitly stated in the information sheet and/or consent form. If risks are foreseen, the researcher should inform participants about where they may obtain support, if necessary. If no risks are foreseen, this should be stated.
2.2. The researcher states that "where applicable" participants can "ask for the data concerning you to be erased (or retained in anonymised form)." The last section in parenthesis should be deleted since it is covered in the clause "where applicable." The researcher is advised to read article 17 of the GDPR to ensure compliance with the patient's right to erasure.
2.3 The information sheet states that "All personal data will be stored securely and separately from any codes to ensure confidentiality". Some elaboration is required to specify where / how the personal data will be securely stored. The researcher should note that password protection does not provide much security for data, therefore any digital identifiable data should be stored in an encrypted manner.
2.4 The researcher should note that, in exceptional circumstances, examiners may need access to raw data for verification purposes. The information sheet and consent form need to be amended to reflect this.

Please forward the **amended documents with track changes** **to Dr Rosienne Farrugia**, in copy, to be approved oBo FREC. **Once the FREC has verified that all the issues raised above have been addressed, you may proceed with your study.**

Please forward me:
1. A soft copy of the documents a), b) and c) **merged in ONE pdf document**:
   a) the revised pages only made in Word using track changes.
   b) the endorsement email from your supervisor.
   c) the endorsement email from Dr Rosienne Farrugia.

2. An updated soft copy of the appendices in a zipped file **(without track changes)**.

by not later than Friday, 30th October.

Thanks and Regards,
Christabel
Christabel Vella
FREC Secretary

Appendix 2: Permission from Data Protection Officer.

SAHHA PRIMARJA

7 Sqaq Harper,
Furjana
FRN 1940

Telephone: + 356 21239993
Telefax: + 356 21222856

Website: http://www.health.gov.mt

PRIMARY HEALTH CARE

7 Harper Lane,
Floriana
FRN 1940

Telephone: +356 21239993
Telefax: +356 21222856

24 April 2020

Matthew Carabott
1, Joelle,
Triq Dun Guzepp Demicoli,
Hal-Ghaxaq
GXQ 2253

Re: Your request to carry out a study within the Primary HealthCare

Dear Mr Carabott,

Your request to carry out the research within the department has been **temporarily granted** on the proviso that you furnish our department with a copy of the approval from the University Research Ethics Committee (UREC) ***prior*** to the actual commencement of your study.

Please be informed that as we have to abide to the Data Protection Law, we cannot provide you with a list of data subjects' (clients/patients/staff) personal contact details so in your methodology you should take this into consideration and make it clear within your application with UREC.*

Following approval from the University Research Ethics Committee we will furnish you with a final permission and you may proceed. If the department does not receive a copy of the approval from the University Research Ethics Committee, this temporary permission to conduct the study/research will automatically be declared as void.

Yours truly,

Dr M. Vella DPO,
F/CEO, Data Controller
Primary HealthCare

May I suggest that you offer the invitation for participation through any officer in charge (e.g. Nursing officer/Principal GP/Podiatrist/physiotherapist/etc).

Appendix 3: Permission from Podiatry Lead.

L-Università ta' Malta

Matthew Carabott <matthew.carabott.13@um.edu.mt>

RE: [EXTERNAL] - URGENT! Approval to recruit participants from Podiatry Clinics at Health Centres

1 message

Scicluna Andrew at Health-Primary Health Care <andrew.scicluna@gov.mt> 10 July 2020 at 07:10
To: Matthew Carabott <matthew.carabott.13@um.edu.mt>

Dear Matthew

No objection

Good luck in your studies

Andrew Scicluna
Professional Lead (Podiatry)
Podiatry
Health-Primary Health Care

t +356 21494969 **e** andrew.scicluna@gov.mt
https://health.gov.mt | www.publicservice.gov.mt | fb.com/servizzpubbliku

MINISTRY FOR HEALTH

B'KARA HEALTH CENTRE, TRIQ TUMAS FENECH,
BIRKIRKARA, MALTA

Appendix 4: Permission from Head of Department to make use of the lab and thermal camera.

L-Università ta' Malta

Matthew Carabott <matthew.carabott.13@um.edu.mt>

Permission to make use of the FLIR 360 thermographic camera and the biomechanics lab

3 messages

Matthew Carabott <matthew.carabott.13@um.edu.mt> 18 April 2020 at 16:36
To: Cynthia Formosa <cynthia.formosa@um.edu.mt>

Dear Dr. Formosa,

I am an M.Sc. student at the University of Malta currently conducting a dissertation entitled "The Application of Thermography as a Screening Tool to Detect Type 2 Diabetic Foot Disease".

The aim of this research is to determine whether the thermographic camera can be used to identify the presence of T2DM complications such as PAD, neuropathy, and neuroischaemia. If T2DM is uncontrolled for a long period of time, damage will be done to the peripheral arteries and nerves leading to complications such as ulcerations, infections and eventually amputations or even death. This research involves the participant lying supine on a podiatry couch for 15 minutes in a temperature-controlled environment and a thermographic image of the soles of the feet is taken. A thermographic image is displayed in a series of colours showing various temperatures. Using only the thermographic image, the researcher will try to determine whether T2DM complications are present. Furthermore, routine diagnostic tests for PAD and neuropathy using a doppler US, 10g monofilament and 128MHz tuning fork will be done. Results from the thermographic images will then be compared to the results from the standard diagnostic tests.

I would like to request your permission to make use of the FLIR 360 thermographic camera and the biomechanics lab to conduct my research

Should you require further information, you can contact me via mobile on 79910593 or email matthew.carabott.13@gov.mt. You can also contact my supervisor, Dr Alfred Gatt via mobile on 23401153 or email alfred.gatt@um.edu.mt.

Thank you in advance.

Regards,
Matthew Carabott

B.Sc. (Hons.) Matthew Carabott

Cynthia Formosa <cynthia.formosa@um.edu.mt> 19 April 2020 at 11:59
To: Matthew Carabott <matthew.carabott.13@um.edu.mt>

Dear Matthew

Thank you for your email. No objection from my end to use the Clinical Biomechanics lab and the necessary equipment required for your study during your studies.

regards

Professor Cynthia Formosa
Professor Cynthia Formosa PhD FFPM RCPS (Glasg.)

Appendix 5: Permission from Intermediary.

L-Università ta' Malta

Matthew Carabott <matthew.carabott.13@um.edu.mt>

Re: [EXTERNAL] - Permission to Act as Intermediary

2 messages

Mizzi Anabelle at Health-Primary Health Care <anabelle.mizzi@gov.mt> 18 April 2020 at 20:10
To: Matthew Carabott <matthew.carabott.13@um.edu.mt>

Dear Matthew,
I can confirm that I am willing to act as an intermediary for your research.

Regards

Anabelle Mizzi

On 18 Apr 2020, at 16:45, Matthew Carabott <matthew.carabott.13@um.edu.mt> wrote:

Dear Ms. Mizzi,

I am an M.Sc. student at the University of Malta currently conducting a dissertation entitled "The Application of Thermography as a Screening Tool to Detect Type 2 Diabetic Foot Disease".

The aim of this research is to determine whether the thermographic camera can be used to identify the presence of T2DM complications such as PAD, neuropathy, and neuroischaemia. If T2DM is uncontrolled for a long period of time, damage will be done to the peripheral arteries and nerves leading to complications such as ulcerations, infections and eventually amputations or even death. This research involves the participant lying supine on a podiatry couch for 15 minutes in a temperature-controlled environment and a thermographic image of the soles of the feet is taken. A thermographic image is displayed in a series of colours showing various temperatures. Using only the thermographic image, the researcher will try to determine whether T2DM complications are present. Furthermore, routine diagnostic tests for PAD and neuropathy using a doppler US, 10g monofilament and 128MHz tuning fork will be done. Results from the thermographic images will then be compared to the results from the standard diagnostic tests.

Your role in this project would be to identify potential participants that can be recruited in this study. All participants should be T2DM and between 18 and 75 years. Both male and female participants are accepted.

Prior to recruitment, you will be kindly required to supply participants with an information sheet containing all details of the study. Thereafter, participants will be required to sign a consent form upon their agreement to participate in the study.

Should you require further information, you can contact me via mobile on 79910593 or email matthew.carabott.13@gov.mt. You can also contact my supervisor, Dr Alfred Gatt via mobile on 23401153 or email alfred.gatt@um.edu.mt.

Thank you in advance for your participation in this research.

Regards,

Appendix 6: Information Letter

Information letter

Matthew Carabott
1, Joelle,
Triq Dun Guzepp Demicoli,
Hal Ghaxaq

Dear participant,

I am an M.Sc. Podiatry student currently conducting a study entitled;

"The Application of Thermography as a Screening Tool to Detect Type 2 Diabetic Foot Disease".

You are being invited to participate in this research, and therefore it is important that you read the following information to be aware what this research involves. Feel free to ask any questions if you need further clarification.

The aim of this research is to determine whether the thermographic camera can be used to identify the presence of T2DM complications such as PAD, neuropathy, and neuroischaemia. This research will benefit patients with T2DM by providing a new way of identifying and preventing complications using this non-contact technique. If T2DM is uncontrolled for a long period of time, damage will be done to the peripheral arteries and nerves leading to complications such as ulcerations, infections, amputations or even death. This research involves the participant lying supine on a podiatry couch for 15 minutes in a temperature-controlled environment and a thermographic image of the soles of the feet is taken. A thermographic image is displayed in a series of colours showing various temperatures. Images of the face or any image that can reveal the identity of the participant will not be taken. Using only the thermographic image, the researcher will try to determine whether T2DM complications are present. Furthermore, routine diagnostic tests for PAD and neuropathy using a doppler US, 10g monofilament and 128MHz tuning fork will be done. The Results from the thermographic images will then be compared to the results from the standard diagnostic tests. The whole duration should not take more than 30 minutes.

Codes will be assigned to the images and all data collected. All personal data will be stored securely and separately from any codes to ensure confidentiality. Only the researcher and the supervisor will have access to the coded data collected. Furthermore, all personal data would

be destroyed upon completion of the research. The identity and personal information of the participant will not be revealed in any publication, presentation or reports of this research.

At least 100 participants will take part in this research.

It is your decision to take part or abstain from this research. If you wish to take part, you will be asked to sign a consent form confirming your willingness to take part in this research. You will be free to withdraw from this study without giving a reason and without effecting your care/treatment.

As a participant, you have the right under the General Data Protection Regulation (GDPR) and national legislation that implements and further specifies the relevant provisions of said regulation to access, rectify, and where applicable ask for the data concerning you to be erased (or retained in anonymised form).

You can keep a copy of this information letter and the consent form if needed.

Ethics approval has been obtained from the university of Malta.

Should you require further information, you can contact me via mobile on 79910593 or email matthew.carabott.13@gov.mt. You can also contact my supervisor, Dr Alfred Gatt via mobile on 23401153 or email alfred.gatt@um.edu.mt.

Thank you in advance for your participation in this research.

Regards,

_____

Matthew Carabott

Appendix 7: Ittra ta' Informazzjoni

Ittra ta' Informazzjoni

Matthew Carabott
1, Joelle,
Triq Dun Gużepp Demicoli,
Ħal Għaxaq

Għażiż Parteċipant,

Jien qed nagħmel *Masters* fil-Podjatrija mal-Universita' ta' Malta bl-isem ta';

"The Application of Thermography as a Screening Tool to Detect Type 2 Diabetic Foot Disease".

Inti qed tingħata ċ-ċans li tipparteċipa f'din ir-riċerka, u għalhekk important li tkun taf din x'tinvolvi. Ħossok liberu li isaqsi mistoqsijiet li jista' jkollok.

L-għan ta` din ir-riċerka huwa biex insiru nafu jekk nistawx nużaw kamera termografika biex nidentifikaw kumplikazzjonijiet tad-dijabete. Dawn jinkludu problemi taċ-ċirkulazzjoni, nervituri jew it-tnejn. Min din ir-riċerka se jibbenifikaw pazjenti bid-dijabete billi niprovdu mod ġdid ta kif nistaw nidentifikaw u niprevenu kumplikazzjonijiet. Jekk id-dijabete ma tkunx ikkontrollata għal perjodu twil ta żmien, l-arterji u n-nervituri fil-periferija issirilhom il-ħsara li jwaslu għal feriti, infezzjonijiet, amputazzjonijiet u saħansitra anki mewt. Din ir-riċerka tinvolvi l-parteċipant jimted fuq il-*couch* għal ħmistax il-minuta f'ambjent b`temperatura kkontrollata. Wara jittieħed ritratt termografiku tal-qiegħ tas-sieq. Ritratt termografiku jkun jinkludi diversi kuluri li jfissru temperaturi differenti. Mhux ser jiġu meħuda ritratti tal-wiċċ jew postijiet oħra li fijhom tista tinkixef l-identita' tal-pazjent. Wara dan, se jsiru ukoll diversi testijiet li jintużaw fil-preżent biex niċċekjaw l-istat tan-nervituri u ċ-ċirkulazzjoni. Dawn it-testijiet se jsiru permezz ta *doppler US, 10g monofilament* u *128MHz tuning fork.* L-istorja tal-pazjent tista tiġi użata biex tinkiseb informazzjoni relatata ma din ir-riċerka. Ir-riċerkatur ser jiprova jidentifika jekk hemmx kumplikazzjonijiet tad-dijabete permezz tar-ritratt termografiku biss. Fl-aħħar ir-riżultat mill-kamera termografika jigi mqabbel mar-riżultati li nġabbru mit-testijiet taċ-ċirkulazzjoni u n-nervituri. Din il-proċedura m'għandiex tieħu iktar minn 30 minuta.

Kodiċi ser jiġu assenjati mar-ritratti u l-informazzjoni kollha miġbura. L-informazzjoni personali kollha se tiġi miżmuma f'post sigur, separatament mill-kodiċi, biex tiġi assigurata l-kunfidenzjalita. L-informazzjoni personali kollha ser tiġi meqruda hekk kif tintem din ir-

riċerka. L-identita' u l-informazzjoni personali tal-parteċipant mhux ser tinkixef f'ebda publikazzjoni, preżentazjoni jew rapport ta din ir-riċerka.

Min tal-inqas 100 parteċipant huma mistenija jieħdu sehem f'din ir-riċerka.

Hija kompletament id-deċiżjoni tiegħek li tieħu sehem jew tastjeni min din ir-riċerka. Jekk tixtieq tieħu sehem, inti ser tiġi mitlub tiffirma formula ta kunsens li turi li inti tixtieq tieħu sehem f'din ir-riċerka. Inti tista twaqqaf il-parteċipazzjoni tiegħek meta trid u mingħajr ma tagħti raġuni, u mingħajr ma taffetwalek il-kura/trattament tiegħek.

Il-parteċipant jista, jżomm kopja tal-ittra t'informazzjoni u l-formola tal-kunsens.

Din ir-riċerka ġiet approvata mill-bord tal-etika tal-Universita' ta' Malta.

Jekk għandek bzonn iktar informazzjoni tista tikkuntatja lili fuq *mobile* 79910593 jew *email* matthew.carabott.13@gov.mt. Tista tikkuntatja ukoll lis-superviżur tieghi, Dr. Alfred Gatt fuq 23401153 jew *email* alfred.gatt@um.edu.mt.

Grazzi bil-quddiem tal-parteċipazzjoni tiegħek f'din ir-riċerka.

Tislijiet,

_____

Matthew Carabott

Appendix 8: Consent Form

I have been asked to participate in the research entitled "The Application of Thermography as a Screening Tool to Detect Type 2 Diabetic Foot Disease".

The aim of this research is to determine whether the thermographic camera can be used to identify the presence of T2DM complications such as PAD, neuropathy, and neuroischaemia. This research will benefit patients with T2DM by proving a new way of identifying and preventing complications using this non-contact technique.

By signing this consent form, I (name and surname) _____, certify that I have read the information letter. Additionally, I have been given a through explanation of the purpose and details of the research by the researcher and any difficulties or queries have been clarified. The total duration of my involvement should not take more than 30 minutes.

I am giving my permission for thermographic images to be taken.

I am aware that results of this study may be used for medical or scientific purpose and that results achieved from this study may be reported or published. However, my identity will not be revealed in any way.

Additionally, I understand that only the researcher and the supervisor will have access to the data collected. Furthermore, all personal data would be destroyed upon completion of the research.

I am under no obligation to participate and I am doing this voluntarily. I can withdraw from the study at any time without giving a reason and without effecting my treatment. I am not receiving any remuneration for participating in this study.

Under the General Data Protection Regulation (GDPR) and national legislation that implements and further specifies the relevant provisions of said regulation the participants have the right to access, rectify, and where applicable erase the data concerning them.

In case of any queries I may contact the researcher, Mr. Carabott on mobile (79910593) or via email (matthew.carabott.13@um.edu.mt), or the supervisor via email (alfred.gatt@um.edu.mt) or on landline (23401153).

The signature below indicates my willingness to take part in this study.

Participant:

_____	_____	_____
Name and Surname	Contact Number	Signature

Researcher:

Matthew Carabott	79910593	_____
Name and Surname	Contact Number	Signature

Supervisor:

Alfred Gatt	23401153	_____
Name and Surname	Contact Number	Signature

Appendix 9: Formola ta` Kunsens

Jien ġejt mitlub nieħu sehem f' riċerka dwar *"The Application of Thermography as a Screening Tool to Detect Type 2 Diabetic Foot Disease"*.

L-għan ta' din ir-riċerka huwa li niddeterminaw jekk il-kamera termografika tistax tintuża biex nikkonfermaw komplikazzjonijiet ikkawżati mid-dijabete, bħal mard arterjali, newropatija u oħrajn. Din ir-riċerka se tkun ta' benefiċċju għall-pazjenti dijabetiċi għaliex fiha se neżaminaw mod ġdid kif jiġu identifikati kumplikazzjonijiet minn qabel ma jiżviluppaw is-sintomi relatati, u b' hekk ikunu jistgħu jiġu prevenuti.

Bil-firma tiegħi fuq din il-formola, jien _____, nikkonferma li ingħatajt spjega dwar l-iskop u d-dettalji dwar din ir-riċerka u l-inolviment tiegħi mir-riċerkatur, u kull dubju jew inċertezza li seta' kien hemm ġiet iċċarata. Il-parteċipazzjoni tiegħi m`għandiex tieħu iktar minn 30 minuta.

Jien nagħti permess biex jittieħdu ritratti bil-kamera termografika.

Jien ukoll konxju mill-fatt li r-riżultati ta' dan l-istudju se jintużaw biss għall-finijiet mediċi u ta' riċerka u li r-riżultati jistgħu jiġu ippublikati. Pero l-identita personali tiegħi mhux se titħabbar taħt l-ebda ċirkostanza.

Nifhem ukoll li kull dettall personali tal-parteċipanti ta' dan l-istudju se jiġi eredikat u mħassar b' mod permanenti hekk kif titlesta r-riċerka.

Nifhem li jien minix obbligat li nipparteċipa u qed nagħmel dan b' mod volontarju. Jien liberu li nwaqqaf is-sehem tiegħi fi x' ħin irrid mingħajr ma nagħti l-ebda raġuni. Minix se nirċievi l-ebda inċentiv monetarju tal-parteċipazzjoni f' dan l-istudju.

F' każ ta domandi jew bżonn ta' kjarifiki, tista' tikkuntattjani permezz tal-*mobile* (79910593) jew b' *email* (matthew.carabott.13@um.edu.mt) jew tista' wkoll tikkuntattja lis-superviżur tiegħi b' *email* (alfred.gatt@um.edu.mt) .

Il-firma hawn taħt tindika r-rieda tiegħi li nieħu sehem f' dan l-istudju.

Parteċipant:

_____ _____ _____

Isem Numru Firma

Riċerkatur:

Matthew Carabott 79910593 _____

Firma

Supervisor:

Dr. Alfred Gatt 23401153 _____

Firma

Appendix 10: Data Collection Sheet

Assessment Sheet

Code Number: _____ **Image Number: _____**

Age: ____ **Gender:_____**

Doppler Wave Form

	Right	Left
Dorsalis Pedis		
Posterior Tibial		

ABPI

	Right	Left
Dorsalis Pedis		
Posterior Tibial		

Neuropathy

	Right		Left	
10g Monofilament				
128 Hz Tuning Fork	Malleolus	1st MTPJ	Malleolus	1st MTPJ

Appendix 11: Average Toe Temperatures, Probability & Actual Presence of Complications

Average Toes Temperature	Probability of Complications	Actual Presence of Complications
24.4	0.398	No
26.6	0.516	No
26.3	0.502	No
25.9	0.478	No
22.1	0.286	No
22.2	0.287	No
23.8	0.364	No
24.2	0.388	No
25.1	0.433	No
24.1	0.379	No
25.8	0.475	No
28.1	0.598	No
27.1	0.543	No
29.1	0.647	No
25.2	0.438	No
25.4	0.452	No
24.8	0.418	No
24.5	0.401	No
25.6	0.463	No
25.7	0.465	No
27.0	0.538	No
28.8	0.636	No
26.5	0.512	No

25.6	0.460	No
27.9	0.586	No
23.6	0.358	No
23.8	0.367	No
24.8	0.416	No
25.0	0.427	No
22.5	0.302	No
22.9	0.322	No
24.2	0.389	No
24.5	0.403	No
22.0	0.280	No
22.2	0.287	No
26.3	0.498	Yes
26.4	0.504	Yes
26.2	0.493	Yes
28.9	0.639	Yes
27.0	0.538	Yes
28.3	0.606	Yes
29.7	0.678	Yes
33.6	0.833	Yes
32.6	0.799	Yes
29.4	0.665	Yes
31.6	0.763	Yes
30.7	0.726	Yes
26.8	0.527	Yes
26.9	0.535	Yes
27.5	0.567	Yes

31.9	0.775	Yes
32.1	0.781	Yes
29.6	0.676	Yes
29.1	0.650	Yes
29.6	0.672	Yes
29.8	0.682	Yes
27.1	0.545	Yes
26.4	0.505	Yes
28.8	0.632	Yes
31.1	0.743	Yes
32.9	0.810	Yes
32.3	0.791	Yes
32.1	0.783	Yes
32.7	0.804	Yes

Appendix 12: Hallux Temperatures, Probability & Actual Presence of Complications

Average Hallux Temperature	Probability of Complications	Actual Presence Complications
25.50	0.456	No
26.70	0.522	No
26.70	0.522	No
26.70	0.522	No
21.80	0.271	No
21.90	0.275	No
24.50	0.402	No
24.00	0.376	No
25.00	0.429	No
24.00	0.376	No
25.80	0.473	No
28.50	0.619	No
27.40	0.560	No
29.50	0.669	No
25.50	0.456	No
24.70	0.413	No
24.60	0.408	No
24.30	0.392	No
25.70	0.467	No
25.60	0.462	No
27.40	0.560	No
29.30	0.659	No
27.90	0.587	No

26.80	0.527	No
27.40	0.560	No
23.60	0.356	No
24.80	0.418	No
25.10	0.434	No
25.20	0.440	No
22.80	0.316	No
23.80	0.366	No
23.90	0.371	No
24.60	0.408	No
22.10	0.284	No
22.30	0.293	No
25.80	0.473	Yes
26.60	0.516	Yes
26.10	0.489	Yes
28.50	0.619	Yes
28.60	0.624	Yes
29.00	0.644	Yes
30.10	0.698	Yes
33.80	0.839	Yes
32.50	0.796	Yes
29.10	0.649	Yes
31.20	0.746	Yes
29.70	0.679	Yes
27.00	0.538	Yes
27.10	0.544	Yes
28.30	0.608	Yes

32.20	0.785	Yes
32.90	0.810	Yes
30.80	0.729	Yes
30.30	0.707	Yes
28.10	0.598	Yes
29.20	0.654	Yes
26.70	0.522	Yes
26.50	0.511	Yes
31.00	0.738	Yes
31.10	0.742	Yes
33.20	0.820	Yes
32.80	0.807	Yes
32.60	0.800	Yes
33.45	0.828	Yes

Appendix 13: 2nd Toe Temperatures, Probability & Actual Presence of Complications

Average 2nd Toe Temperature	Probability of T2DM Complications	Actual Presence Complications
24.70	0.413	No
27.10	0.544	No
26.30	0.500	No
26.00	0.484	No
21.90	0.275	No
21.90	0.275	No
23.30	0.341	No
23.80	0.366	No
25.00	0.429	No
23.80	0.366	No
25.50	0.456	No
28.30	0.608	No
27.40	0.560	No
29.00	0.644	No
24.80	0.418	No
26.00	0.484	No
24.40	0.397	No
24.10	0.381	No
25.50	0.456	No
25.70	0.467	No
27.40	0.560	No
28.60	0.624	No
25.80	0.473	No

24.90	0.424	No
27.60	0.571	No
23.30	0.341	No
23.50	0.351	No
24.60	0.408	No
24.80	0.418	No
22.50	0.302	No
23.00	0.326	No
24.00	0.376	No
24.40	0.397	No
21.80	0.271	No
22.00	0.280	No
25.70	0.467	Yes
27.00	0.538	Yes
25.90	0.478	Yes
29.20	0.654	Yes
26.50	0.511	Yes
30.50	0.716	Yes
33.40	0.827	Yes
32.20	0.785	Yes
28.30	0.608	Yes
32.00	0.778	Yes
31.00	0.738	Yes
26.30	0.500	Yes
26.50	0.511	Yes
27.70	0.576	Yes
31.20	0.746	Yes

31.50	0.758	Yes
30.00	0.693	Yes
29.90	0.688	Yes
29.10	0.649	Yes
29.70	0.679	Yes
27.10	0.544	Yes
26.40	0.505	Yes
28.10	0.598	Yes
31.10	0.742	Yes
32.80	0.807	Yes
32.30	0.789	Yes
31.80	0.770	Yes
32.40	0.793	Yes

Appendix 14: 3rd Toe Temperatures, Probability & Actual Presence of Complications

3rd Toe Temperature	Probability of T2DM Complications	Actual Presence Complications
24.30	0.392	No
26.70	0.522	No
26.30	0.500	No
25.70	0.467	No
22.10	0.284	No
22.00	0.280	No
23.70	0.361	No
24.20	0.387	No
25.00	0.429	No
23.90	0.371	No
25.70	0.467	No
28.30	0.608	No
27.10	0.544	No
28.70	0.629	No
24.80	0.418	No
25.80	0.473	No
24.70	0.413	No
24.50	0.402	No
25.60	0.462	No
25.50	0.456	No
27.00	0.538	No
28.80	0.634	No
25.70	0.467	No

24.80	0.418	No
28.30	0.608	No
23.50	0.351	No
24.10	0.381	No
24.50	0.402	No
24.80	0.418	No
22.40	0.298	No
22.80	0.316	No
24.20	0.387	No
24.30	0.392	No
21.90	0.275	No
22.00	0.280	No
26.60	0.516	Yes
26.20	0.495	Yes
25.90	0.478	Yes
29.60	0.674	Yes
26.50	0.511	Yes
27.90	0.587	Yes
29.50	0.669	Yes
33.60	0.833	Yes
32.80	0.807	Yes
28.80	0.634	Yes
31.40	0.754	Yes
30.50	0.716	Yes
26.70	0.522	Yes
26.80	0.527	Yes
27.20	0.549	Yes

31.80	0.770	Yes
32.10	0.782	Yes
29.10	0.649	Yes
29.10	0.649	Yes
30.50	0.716	Yes
30.00	0.693	Yes
27.50	0.566	Yes
26.50	0.511	Yes
28.40	0.613	Yes
31.60	0.762	Yes
32.90	0.810	Yes
32.20	0.785	Yes
32.00	0.778	Yes
32.30	0.789	Yes

Appendix 15: 4th Toe Temperatures, Probability & Actual Presence of Complications

4th Toe Temperature	Probability of T2DM Complications	Actual Presence Complications
24.10	0.381	No
26.30	0.500	No
26.30	0.500	No
25.60	0.462	No
22.40	0.298	No
22.50	0.302	No
23.80	0.366	No
24.50	0.402	No
25.10	0.434	No
24.10	0.381	No
26.00	0.484	No
28.00	0.592	No
27.00	0.538	No
29.00	0.644	No
25.10	0.434	No
25.40	0.451	No
25.00	0.429	No
24.70	0.413	No
25.70	0.467	No
25.70	0.467	No
26.80	0.527	No
28.80	0.634	No
26.30	0.500	No

25.40	0.451	No
27.50	0.566	No
23.60	0.356	No
23.50	0.351	No
24.60	0.408	No
24.90	0.424	No
22.40	0.298	No
22.60	0.307	No
24.50	0.402	No
24.70	0.413	No
22.10	0.284	No
22.30	0.293	No
26.40	0.505	Yes
26.20	0.495	Yes
26.40	0.505	Yes
28.30	0.608	Yes
26.60	0.516	Yes
28.00	0.592	Yes
29.60	0.674	Yes
33.70	0.836	Yes
32.80	0.807	Yes
30.30	0.707	Yes
31.20	0.746	Yes
31.00	0.738	Yes
26.90	0.533	Yes
26.80	0.527	Yes
27.00	0.538	Yes

32.10	0.782	Yes
31.20	0.746	Yes
29.10	0.649	Yes
28.60	0.624	Yes
30.20	0.702	Yes
30.10	0.698	Yes
27.20	0.549	Yes
26.70	0.522	Yes
28.30	0.608	Yes
31.50	0.758	Yes
33.00	0.814	Yes
32.20	0.785	Yes
32.10	0.782	Yes
32.45	0.795	Yes

Appendix 16: 5th Toe Temperatures, Probability & Actual Presence of Complications

Average 5th Toe Temperature	Probability of T2DM Complications	Actual Presence Complications
23.50	0.351	No
26.20	0.495	No
26.10	0.489	No
25.50	0.456	No
22.50	0.302	No
22.50	0.302	No
23.50	0.351	No
24.60	0.408	No
25.30	0.445	No
24.50	0.402	No
26.20	0.495	No
27.40	0.560	No
26.50	0.511	No
29.10	0.649	No
25.60	0.462	No
25.20	0.440	No
25.30	0.445	No
24.80	0.418	No
25.60	0.462	No
25.80	0.473	No
26.40	0.505	No
28.70	0.629	No
26.90	0.533	No

26.00	0.484	No
28.60	0.624	No
24.20	0.387	No
23.20	0.336	No
25.00	0.429	No
25.10	0.434	No
22.40	0.298	No
22.40	0.298	No
24.60	0.408	No
24.60	0.408	No
22.10	0.284	No
22.20	0.289	No
26.80	0.527	Yes
25.90	0.478	Yes
26.60	0.516	Yes
28.90	0.639	Yes
26.80	0.527	Yes
28.10	0.598	Yes
28.70	0.629	Yes
33.50	0.830	Yes
32.50	0.796	Yes
30.60	0.720	Yes
32.30	0.789	Yes
31.50	0.758	Yes
27.10	0.544	Yes
27.50	0.566	Yes
27.40	0.560	Yes

32.30	0.789	Yes
32.70	0.803	Yes
29.20	0.654	Yes
27.70	0.576	Yes
29.90	0.688	Yes
29.80	0.684	Yes
27.10	0.544	Yes
25.90	0.478	Yes
28.00	0.592	Yes
30.30	0.707	Yes
32.60	0.800	Yes
32.20	0.785	Yes
32.10	0.782	Yes
33.05	0.815	Yes

Appendix 17: Average Forefoot Temperatures, Probability & Actual Presence of Complications

Temperature	Probability of Complications	Actual Presence Complications
25.43	0.380	No
27.20	0.490	No
27.77	0.526	No
27.47	0.507	No
23.70	0.283	No
23.90	0.294	No
25.20	0.366	No
25.73	0.398	No
26.57	0.450	No
25.90	0.408	No
27.30	0.496	No
29.13	0.611	No
28.47	0.570	No
30.73	0.702	No
27.80	0.528	No
27.80	0.528	No
26.53	0.448	No
26.20	0.427	No
27.63	0.517	No
27.77	0.526	No
29.27	0.619	No
30.13	0.669	No
29.47	0.631	No

29.87	0.654	No
28.97	0.601	No
25.00	0.355	No
24.73	0.339	No
26.63	0.454	No
27.20	0.490	No
24.80	0.343	No
24.77	0.341	No
25.13	0.362	No
25.50	0.384	No
23.63	0.279	No
24.07	0.303	No
27.83	0.530	Yes
27.50	0.509	Yes
27.43	0.505	Yes
28.87	0.595	Yes
28.47	0.570	Yes
30.30	0.679	Yes
31.20	0.726	Yes
32.70	0.795	Yes
32.30	0.778	Yes
30.70	0.700	Yes
31.60	0.746	Yes
31.27	0.730	Yes
28.77	0.589	Yes
29.53	0.635	Yes
29.30	0.621	Yes

32.37	0.781	Yes
32.67	0.794	Yes
31.07	0.720	Yes
30.67	0.699	Yes
31.17	0.725	Yes
31.93	0.762	Yes
28.90	0.597	Yes
27.83	0.530	Yes
30.00	0.662	Yes
31.37	0.735	Yes
33.27	0.818	Yes
33.10	0.811	Yes
30.90	0.711	Yes
31.77	0.754	Yes

Appendix 18: 1st MTH Temperatures, Probability & Actual Presence of Complications

Average 1st MTH Temperature	Probability of T2DM of Complications	Actual Presence of Complications
25.80	0.402	No
27.60	0.515	No
28.00	0.541	No
28.00	0.541	No
23.70	0.283	No
23.80	0.288	No
25.30	0.372	No
26.10	0.421	No
26.70	0.458	No
26.00	0.415	No
27.50	0.509	No
29.30	0.621	No
28.70	0.584	No
31.00	0.716	No
28.00	0.541	No
28.50	0.572	No
26.60	0.452	No
26.40	0.439	No
27.60	0.515	No
27.80	0.528	No
29.20	0.615	No
30.60	0.695	No
29.10	0.609	No

29.70	0.644	No
28.70	0.584	No
25.00	0.355	No
25.00	0.355	No
26.70	0.458	No
27.30	0.496	No
24.70	0.337	No
26.20	0.427	No
25.10	0.360	No
25.50	0.384	No
23.50	0.273	No
24.10	0.304	No
27.50	0.509	Yes
27.90	0.534	Yes
27.50	0.509	Yes
28.60	0.578	Yes
28.70	0.584	Yes
30.60	0.695	Yes
31.40	0.736	Yes
32.90	0.803	Yes
32.60	0.791	Yes
30.50	0.690	Yes
31.40	0.736	Yes
31.40	0.736	Yes
28.90	0.597	Yes
29.30	0.621	Yes
29.60	0.639	Yes

32.30	0.778	Yes
32.60	0.791	Yes
31.00	0.716	Yes
31.40	0.736	Yes
30.90	0.711	Yes
31.50	0.741	Yes
29.00	0.603	Yes
28.20	0.553	Yes
30.60	0.695	Yes
31.30	0.731	Yes
33.50	0.826	Yes
33.70	0.834	Yes
30.90	0.711	Yes
32.10	0.769	Yes

Appendix 19: 3rd MTH Temperatures, Probability & Actual Presence of Complications

Average 3rd MTH Temperature	Probability of Complications	Actual Presence of Complications
25.70	0.396	No
27.60	0.515	No
27.90	0.534	No
27.50	0.509	No
23.70	0.283	No
24.10	0.304	No
25.30	0.372	No
25.60	0.390	No
26.60	0.452	No
25.90	0.408	No
27.20	0.490	No
29.30	0.621	No
28.70	0.584	No
30.80	0.706	No
28.20	0.553	No
28.10	0.547	No
26.60	0.452	No
26.30	0.433	No
27.90	0.534	No
27.90	0.534	No
29.50	0.633	No
30.50	0.690	No
29.40	0.627	No

30.20	0.673	No
29.20	0.615	No
25.00	0.355	No
24.90	0.349	No
26.50	0.446	No
27.50	0.509	No
25.10	0.360	No
24.10	0.304	No
25.20	0.366	No
25.60	0.390	No
23.70	0.283	No
24.30	0.315	No
27.90	0.534	Yes
27.50	0.509	Yes
27.30	0.496	Yes
28.90	0.597	Yes
28.60	0.578	Yes
30.30	0.679	Yes
31.30	0.731	Yes
32.80	0.799	Yes
32.40	0.783	Yes
30.90	0.711	Yes
31.70	0.751	Yes
31.40	0.736	Yes
28.90	0.597	Yes
29.60	0.639	Yes
29.60	0.639	Yes

32.40	0.783	Yes
32.90	0.803	Yes
31.20	0.726	Yes
30.70	0.700	Yes
31.10	0.721	Yes
32.20	0.774	Yes
29.20	0.615	Yes
28.10	0.547	Yes
30.10	0.667	Yes
31.70	0.751	Yes
33.70	0.834	Yes
33.30	0.819	Yes
30.70	0.700	Yes
31.50	0.741	Yes

Appendix 20: 5th MTH Temperatures, Probability & Actual Presence of Complications

5th MTH Temperature	Probability of Complications	Actual Presence Complications
24.80	0.343	No
26.40	0.439	No
27.40	0.503	No
26.90	0.471	No
23.70	0.283	No
23.80	0.288	No
25.00	0.355	No
25.50	0.384	No
26.40	0.439	No
25.80	0.402	No
27.20	0.490	No
28.80	0.591	No
28.00	0.541	No
30.40	0.684	No
27.20	0.490	No
26.80	0.465	No
26.40	0.439	No
25.90	0.408	No
27.40	0.503	No
27.60	0.515	No
29.10	0.609	No
29.30	0.621	No
29.90	0.656	No

29.70	0.644	No
29.00	0.603	No
25.00	0.355	No
24.30	0.315	No
26.70	0.458	No
26.80	0.465	No
24.60	0.332	No
24.00	0.299	No
25.10	0.360	No
25.40	0.378	No
23.70	0.283	No
23.80	0.288	No
28.10	0.547	Yes
27.10	0.484	Yes
27.50	0.509	Yes
29.10	0.609	Yes
28.10	0.547	Yes
30.00	0.662	Yes
30.90	0.711	Yes
32.40	0.783	Yes
31.90	0.760	Yes
30.70	0.700	Yes
31.70	0.751	Yes
31.00	0.716	Yes
28.50	0.572	Yes
29.70	0.644	Yes
28.70	0.584	Yes

32.40	0.783	Yes
32.50	0.787	Yes
31.00	0.716	Yes
29.90	0.656	Yes
31.50	0.741	Yes
32.10	0.769	Yes
28.50	0.572	Yes
27.20	0.490	Yes
29.30	0.621	Yes
31.10	0.721	Yes
32.60	0.791	Yes
32.30	0.778	Yes
31.10	0.721	Yes
31.70	0.751	Yes