PATTERN AND DISTRIBUTION OF PERIPHERAL ARTERIAL DISEASE IN DIABETIC PATIENTS WITH CRITICAL LIMB ISCHEMIA (RUTHERFORD CLINICAL CATEGORY 4-6)
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PATTERN AND DISTRIBUTION OF PERIPHERAL ARTERIAL DISEASE IN DIABETIC PATIENTS WITH CRITICAL LIMB ISCHEMIA (RUTHERFORD CLINICAL CATEGORY 4-6)

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HREC REF: 700/2013

Submitted in fulfilment of the requirements for the degree:
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Date of submission: 20/04/2015

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I, Dr. Mpapho Motsumi, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

I empower the university to reproduce for the purpose of research either the whole or any portion of the contents in any manner whatsoever.

Signature: [Signed]

Date: 21/04/2015
3. ACKNOWLEDGMENTS

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To Prof. D. Kahn, who tirelessly insured that the work is getting done, and who often offered heart-warming support as head of department.

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To the entire vascular department I express my gratitude for your input in making this work possible. It is through your work and commitment that I managed to write this paper. Commendable teamwork.

To my fellow registrars in the department of surgery, your direct and indirect support will not go unnoticed. You made the environment conducive for the work to be done.

4. DEDICATION

My deeply felt gratitude goes to my wife (Dr. Marang Molotsi) and my daughter (Palesa Motsumi) for being there at all times and being so caring and loving. You sacrificed a lot to make this possible. Without your support it wouldn’t have been possible.
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<th>Description</th>
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<tbody>
<tr>
<td>AA</td>
<td>Arcuate artery</td>
</tr>
<tr>
<td>AORTA</td>
<td>Infrarenal Aorta</td>
</tr>
<tr>
<td>ATA</td>
<td>Anterior tibial artery</td>
</tr>
<tr>
<td>CFA</td>
<td>Common femoral artery</td>
</tr>
<tr>
<td>CIA</td>
<td>Common iliac artery</td>
</tr>
<tr>
<td>CLI</td>
<td>Critical limb ischemia</td>
</tr>
<tr>
<td>DM</td>
<td>Diabetes Mellitus</td>
</tr>
<tr>
<td>DP</td>
<td>Dorsalis pedis</td>
</tr>
<tr>
<td>DSA</td>
<td>Digital subtraction angiography</td>
</tr>
<tr>
<td>DYS</td>
<td>Dyslipidemia</td>
</tr>
<tr>
<td>EIA</td>
<td>External iliac artery</td>
</tr>
<tr>
<td>EXSMOK</td>
<td>Ex-smoker</td>
</tr>
<tr>
<td>F</td>
<td>Female</td>
</tr>
<tr>
<td>FEM-POP</td>
<td>Femoropopliteal segment</td>
</tr>
<tr>
<td>HPT</td>
<td>Hypertension</td>
</tr>
<tr>
<td>IIA</td>
<td>Internal iliac artery</td>
</tr>
<tr>
<td>LPA</td>
<td>Lateral plantar artery</td>
</tr>
<tr>
<td>M</td>
<td>Male</td>
</tr>
<tr>
<td>MPA</td>
<td>Medial plantar artery</td>
</tr>
<tr>
<td>N0</td>
<td>Null hypothesis</td>
</tr>
<tr>
<td>PAD</td>
<td>Peripheral arterial disease</td>
</tr>
<tr>
<td>PASS</td>
<td>Power Analysis and Sample Size</td>
</tr>
<tr>
<td>PER</td>
<td>Peroneal artery</td>
</tr>
<tr>
<td>PFA</td>
<td>Profunda femoris artery</td>
</tr>
<tr>
<td>POP</td>
<td>Popliteal artery</td>
</tr>
<tr>
<td>PTA</td>
<td>Posterior tibial artery</td>
</tr>
<tr>
<td>SFA</td>
<td>Superficial femoral artery</td>
</tr>
<tr>
<td>SMOK</td>
<td>Smoker</td>
</tr>
<tr>
<td>TIBIO-PER</td>
<td>Tibioperoneal segment</td>
</tr>
<tr>
<td>TPA</td>
<td>Tibioperoneal artery</td>
</tr>
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</table>
6. DEFINITION OF TERMS

**Major Risk Factor Combination groups**

<table>
<thead>
<tr>
<th>Group</th>
<th>Description</th>
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<tbody>
<tr>
<td>Group 1</td>
<td>DM, HPT, Dyslipidemia</td>
</tr>
<tr>
<td>Group 2</td>
<td>DM, HPT, dyslipidemia, ex-smoker</td>
</tr>
<tr>
<td>Group 3</td>
<td>DM, HPT, dyslipidemia, smoker</td>
</tr>
</tbody>
</table>

**Ex-smoker**  Stopped smoking for a period of more than three months without relapse.

**Patency grading system**

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category 1</td>
<td>Widely patent (Angiographic image with clean pristine edges)</td>
</tr>
<tr>
<td>Category 2</td>
<td>Diffusely diseased but patent (Shaggy edges but no obvious stenosis)</td>
</tr>
<tr>
<td>Category 3</td>
<td>Haemodynamically insignificant occlusive lesions (Areas with &lt;50% stenosis)</td>
</tr>
<tr>
<td>Category 4</td>
<td>Haemodynamically significant occlusive lesions (Areas with ≥ 50% stenosis)</td>
</tr>
<tr>
<td>Category 5</td>
<td>Arterial occlusion (segmental or complete)</td>
</tr>
</tbody>
</table>

**Foot arterial status**

<table>
<thead>
<tr>
<th>Status</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete</td>
<td>The anastomosis between the lateral plantar and the dorsalis pedis is intact filling the metatarsal and digital arteries. The anastomosis between the two arteries is</td>
</tr>
<tr>
<td>Incomplete</td>
<td>not observed</td>
</tr>
<tr>
<td>Absent</td>
<td>No visualized foot arch</td>
</tr>
</tbody>
</table>
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<tr>
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<td>34</td>
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</table>
9. ABSTRACT

**Background** The literature tends to support the notion that diabetic patients typically suffer from tibio-peroneal artery occlusive disease (1) (2) (11) (5) (10) (8) with relative sparing of the foot arteries (1). This study seeks to investigate the pattern and distribution of peripheral artery occlusive disease and the arterial foot arch status in diabetic patients with critical limb ischaemia.

**Methods:** This is a one year prospective study (January 2014 to December 2014) carried out on consecutive patients seen at Groote Schuur Hospital, Vascular Department. The inclusion criteria is: diabetic patients ≥18 years of age with critical limb ischemia who had pre- and post-intervention vascular imaging. The calculated minimum sample size of 63 limbs [756 patency levels (63x12)] was needed to achieve a power of 86% to detect a difference of 0.1900 (19%) with a target significance level of 0.05 (using PASS 11 software). The equality of distribution of categories was analyzed using the One sample Chi-square test (SPSS 22) with our Null hypothesis (N0) assuming that categories occur with equal proportions. In this case categories refers to the 5 patency levels used in this study. All 12 main arteries from infra-renal aorta to crural arteries had their patency levels graded from category 1 to category 5 (widely patent to occluded). The findings were then stratified according to gender, age group (<40 years, 40-54 years and ≥ 55 years) and risk factor combinations [**Group 1** = (DM, HPT, Dyslipidemia); **Group 2** = (DM, HPT, dyslipidemia, exsmoker); **Group 3** = (DM, HPT, dyslipidemia, smoker)]. The three risk combination groups formed the majority of our study group (79%).

**Results:** Seventy-one patients were analyzed: 38/71 females and 33/71 males. Eight hundred and twenty (820) patency categories were recorded [8 patients did not have their aorto-iliac segment imaged (8x4=32)]. There were relatively more category 5 and category 4 (occlusions and high grade-stenosis) patency levels in the tibioperoneal segment with statistically significant disproportion (P <.001 for both categories). However it is worth noting that females had relatively less severe grades of occlusive disease proximally compared to males (females recorded no occlusions in the aortoiliac segment vs 6 recorded for males). Group 3 have a different distribution pattern, with a disproportionate distribution of occlusions (P<0.001) with more occlusions in the femoropopliteal segment followed by tibioperoneal segment. Group 1 and group 2 had disproportionately more occlusions to distal segment (P<0.001). Patients over the age of 55 also had disproportionately more occlusions distally (P<0.001). The majority of our patients are within this age group. Only 10/71 patients had an absent foot arch; 28/71 patients had an incomplete foot arch; 31/71 had a complete foot arch and 2/71 had a poorly imaged foot arch. There was a statistically significant disproportionate distribution (P = 0.004) with the majority of patients having a complete foot arch (Fig 1.12). However on stratifying patients according to gender it became clear that it is female diabetic patients who predominantly had a complete foot arches (22/37;59%) (P=0.004). Male patients predominantly had an incomplete arch (17/32;53% (P =0.048)). Group 2 patients had predominantly complete foot arches 9/13 . For group 1 and group 3 the proportions in the arterial arch status categories were almost the same with slight predominance of incomplete foot arch, followed by complete arch (P<0.05)- Fig 1.15.

**Conclusion:** Diabetic patients in general have severe tibio-peroneal disease. Gender and patients older than 40 years have the same disproportionate distribution of severe lesions to distal segments. However female patients have less severe disease. Group 3 patients have a disproportionate distribution of occlusions (P<0.001) with more occlusions in the femoropopliteal segment. Group 1 and group 2 had a disproportionate distribution of occlusions (category 5) to distal segment (P<0.001). Female diabetics tends to have a complete arterial foot arch (P=0.004) as opposed to male patients who have predominantly incomplete foot arches (P=0.048). Group 2 have predominantly complete arterial foot arch while group 1 and group 3 predominantly have an incomplete arterial foot arch. The predominant age group (≥55) also have a predominantly complete arterial foot arch (P=0.028).
10. INTRODUCTION

The literature tends to support the notion that diabetic patients typically suffer from tibio-peroneal artery occlusive disease (1) (2) (11) (5) (10) (8) with relative sparing of the foot arteries (1). A few studies dispute this notion of severe distal segment involvement in diabetic patients (3) and the arterial foot arch sparing (3) (2). These observations have enormous implications relating to revascularization procedures, bypass graft patencies, limb salvage, healing of ischaemic foot lesions and, to a lesser extent, feasibility of pedal artery bypass procedures when indicated. Studies have looked at the impact of quality of the arterial foot arch and the angiosome revascularization on below knee bypass outcomes as well as foot ulcer healing rate(17)(18). The findings were statistically significant association between rate of foot ulcer healing and quality of the arterial foot arch (17)(18). The predominant impression from the literature review is that there is no association between the quality of the arterial foot arch and the amputation free survival or graft patency rates. It is relevant to stratify diabetic patients according to their risk factor profile, age group and gender when assessing the pattern and distribution of peripheral arterial occlusive disease (PAD). This study set out to investigate the pattern and distribution of peripheral artery occlusive disease and the arterial foot arch status in diabetic patients with critical limb ischaemia. The findings were then stratified according to:

- Gender.
- Age group (<40 years, 40-54 years and ≥ 55 years).
- Risk factor profile (diabetes, hypertension, dyslipidemia, smoking, ex-smoker).

11. AIM

The aim of this study is to study the pattern and distribution of Peripheral arterial disease in diabetic patients with critical limb Ischemia Rutherford category 4 – 6 and to stratify the pattern and distribution according to their atherosclerosis risk factor profile and age group and gender.
LITERATURE REVIEW

Peripheral Arterial Disease:

Overview

Peripheral artery occlusive disease, also commonly known as peripheral artery disease (PAD) is characterized by occlusive atherosclerotic disease of peripheral arteries. It causes significant morbidity and mortality. It is a global challenge and consumes a lot of resources. The impact of PAD is more in the lower extremities. Its management is a constant challenge to the vascular surgeons. The worldwide prevalence of this disease still remains unclear. In the USA it is estimated that 8 to 12 million people are affected by PAD (33). PAD is clearly more prevalent in the elderly population. It is a progressive disease with a clinical picture ranging from asymptomatic to symptomatic. The majority of patients have a subclinical disease (asymptomatic).

PAD is associated with shortened survival mainly due to its systemic effects on multiple organs (heart, brain, kidneys etc.).

Epidemiology

The worldwide prevalence of peripheral artery occlusive disease remains unclear. The prevalence in the USA is estimated at 8 to 12 million (32). PAD is less common in women than it is in men (36). It occurs earlier in men than in women (35). It is more prevalent in the aging populations. A recent systematic review of 34 studies looked at “Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: a systematic review and analysis” (33). The following were the findings:

- Globally there were 202 million people in 2010 with PAD. Of these
  - 69.7% were in the low-income or middle-income countries: prevalence in southeast Asia being 54.8 million and western Pacific Region having a prevalence of 45.9 million in the.
- There was an increase in prevalence of PAD during the preceding decade by 28.7% in low-income or middle-income countries and 13.1% in high-income countries.

Therefore the prevalence of PAD continues to rise.
Pathogenesis

The arterial atherogenesis is a complex process that is driven by an interaction between different processes some of which are poorly understood. The evolution of the atherosclerotic plaque follows a response to an injury to the normal vascular endothelial cells culminating in formation of a thrombus and ultimately angiogenesis and neovascularization. The atherosclerotic plaque thus formed can be:

1. **Unstable (high-risk) plaque:** which is associated with a high risk of rupture and distal embolization causing acute embolic events or acute intraluminal thrombosis leading to arterial occlusion. It has a thin fibrous cap.

2. **Stable plaque:** It has a stable fibrous cap. It is not ulcerated and therefore is less likely to rupture and cause embolic events or acute occlusion of the artery by intraluminal thrombosis. However it still has the potential to progress to symptomatic disease.

![Fig 1.00 Atherosclerotic plaque formation](image-url)
Risk Factors

The atherosclerosis risk factors can be grouped into modifiable and non-modifiable risk factors.

Four main modifiable conventional atherosclerotic risk factors are:

- hypertension,
- hypercholesterolemia,
- diabetes,
- smoking.

Non-modifiable risk factors are

- Age
- Gender
- Ethnicity
- Family history

Very often one of these risk factors are present at the time of diagnosis of peripheral arterial disease. Age is a major non-modifiable risk factor. Risk factor modification is a key component of PAD management(34)(35).

The results of a study published in 2004(45) looking at the association of risk factors with PAD using logistic regression analysis is summarized in the table below:

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>OR (Association with PAD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Black race</td>
<td>2.83</td>
</tr>
<tr>
<td>Current smoking</td>
<td>4.46</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.71</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.75</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>1.68</td>
</tr>
<tr>
<td>Poor kidney function</td>
<td>2.00</td>
</tr>
</tbody>
</table>

*Table 1.a Odds ratio for risk factor association with PAD.*

These are compelling results and it is highly unlikely such associations could have occurred by chance alone.
**Screening**

The most commonly used screening test is resting ABI (34)(35). It is easy to do, cheap, more acceptable to patients and safe.

The ABI calculation: \[\text{(systolic blood pressure at the ankle)} / \text{(brachial artery systolic blood pressure obtained while patient is lying down)}\]

Interpretation: ABI <1 (usually quoted as <0.9) is considered abnormal and usually used to diagnose PAD.

There is no evidence showing benefit in ABI screening of asymptomatic patients(36)(37). A recent(2013) literature review by USPSTF (U.S. Preventive Services Task Force) concluded that there is insufficient evidence to assess the benefit of screening adults with ABI.

It is worth mentioning that ABI as a screening tool has its shortcomings in diabetic patients mainly because the calcified arteries lead to falsely normal or elevated Doppler pressures in this group of patients (46).

**Natural history of PAD:**

The understanding of progression of PAD from the asymptomatic (but having an abnormal ABI) to symptomatic disease is key for managing these group of patients. The literature shows that when asymptomatic patients are followed over a period of five years, 7-15% of them will develop symptoms. This was consistently found in two studies(38)(39). Patient with asymptomatic PAD are still at risk of developing other atherosclerosis associated events.

**Symptomatic PAD**

Symptomatic patients can present as intermittent claudication, critical limb ischemia or may present as an acute limb ischemia.

- **Critical limb ischemia**: “The European Consensus defines critical limb ischemia as rest pain for more than two weeks, or ulceration/gangrene, and an ankle pressure of <50 mmHg or a toe pressure of <30 mmHg”.

- **Acute limb ischemia** “The revised (2007) TASC Inter-Society Consensus defines acute leg ischaemia (ALI) as any sudden decrease in limb perfusion causing a potential threat to limb viability”

There are two main classifications of PAD based on its severity:
• Fontaine classification

<table>
<thead>
<tr>
<th>Fontaine stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td>II</td>
<td>Intermittent claudication</td>
</tr>
<tr>
<td>III</td>
<td>Rest pain</td>
</tr>
<tr>
<td>IV</td>
<td>Tissue loss</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grade</th>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td>I</td>
<td>1</td>
<td>Mild claudication</td>
</tr>
<tr>
<td>I</td>
<td>2</td>
<td>Moderate claudication</td>
</tr>
<tr>
<td>I</td>
<td>3</td>
<td>Severe claudication</td>
</tr>
<tr>
<td>II</td>
<td>4</td>
<td>Ischemic rest pain</td>
</tr>
<tr>
<td>II</td>
<td>5</td>
<td>Minor tissue loss</td>
</tr>
<tr>
<td>III</td>
<td>6</td>
<td>Major tissue loss</td>
</tr>
</tbody>
</table>

• Rutherford classification

Table 1.b Fontaine classification of PAD severity

Follow-up studies have shown that half of the claudicants remain stable (no deterioration of symptomatology) at 5 years or improve. One quarter of the claudicants will experience deterioration in walking distance over 5 years(40). About 5% of those who will experience deterioration in walking distance will experience worsening of symptoms severe enough to require revascularization and about 1% of them will end up with an amputation(41).

The overall outcome in patients with critical limb ischemia is very poor.

Diagnostic Test

The diagnostic test according to ACCF/AHA Practice Guidelines:

“2011 Updated Recommendation: The resting ABI should be used to establish the lower extremity PAD diagnosis in patients with suspected lower extremity PAD, defined as individuals with 1 or more of the following:

• exertional leg symptoms,
- non-healing wounds,
- age 65 and older, or 50 years and older with a history of smoking or diabetes. (Level of Evidence: 1B)

**Pulse volume recordings** are reasonable to establish the initial lower extremity PAD diagnosis, assess localization and severity, and follow the status of lower extremity revascularization procedures. *(Level of Evidence: 2B)*

**Continuous-wave Doppler ultrasound** blood flow measurements are useful to provide an accurate assessment of lower extremity PAD location and severity, to follow lower extremity PAD progression, and to provide quantitative follow-up after revascularization procedures. *(Level of Evidence: 1B)*

Treadmill Exercise Testing With and Without ABI Assessments and 6-Minute Walk Test

**Duplex ultrasound** of the extremities is useful to diagnose anatomic location and degree of stenosis of PAD. *(Level of Evidence: 1A)*

**Contrast Angiography:** Contrast angiography provides detailed information about arterial anatomy and is recommended for evaluation of patients with lower extremity PAD when revascularization is contemplated. *(Level of Evidence: 1B).*

**Treatment of PAD**

Treatment of PAD disease requires a multidisciplinary approach.

Below are a list of components of the management scheme for patients with PAD.

- Cardiovascular Risk Reduction
  - Lipid-Lowering Drugs
  - Antihypertensive Drugs
  - Diabetes Therapies
  - Smoking Cessation
  - Antiplatelet and Antithrombotic Drugs
- Exercise and Lower Extremity PAD Rehabilitation
- Endovascular Treatment for Claudication
- Surgery for Claudication (Open surgery)

**Outcomes of PAD**

It is estimated that of claudicants:

- Approximately 50% will have symptomatic improvement
25% will remain stable
25% will have symptomatic deterioration
5% will need revascularization
1-2% will require ablative therapy in the form of major amputation
50% of claudicants will be dead during 10 years follow-up.

Of every 100 claudicants 1 will progress to critical limb ischemia

For patient with critical limb ischemia

- 20-25% of patients will die within a year of follow up.
- Half of them will be dead at 5 years of follow up.

**CRITICAL LIMB ISCHEMIA IN DIABETIC PATIENTS:**

**Overview**

Diabetes is one of the main risk factors of developing PAD. The global prevalence of diabetes is estimated at 366 million people. Peripheral arterial disease is a known cause of morbidity and mortality in diabetic patients worldwide. It is a problem that needs well-coordinated multidisciplinary approach (43) to manage. Some studies have shown a higher risk of PAD in Hispanic American and African American with diabetes(44). The systemic impact of atherosclerosis in is more pronounced in diabetic patients.

**Pattern and distribution of PAD in DM patients**

With the advent of DSA observant researchers noted a unique pattern and distribution of occlusive arterial disease in diabetic patients with critical limb ischemia. The impression they got was that diabetic patients had more occlusions in their distal arterial segments compared to nondiabetic patients (1)(2)(5)(11).

Karacagil S. et al (1) also noted an association between severe involvement of the foot arteries and severe involvement of tibioperoneal arteries. In his study published in 1989 he observed tibioperoneal occlusions in 71% of the diabetic patients compared to 52% of the non-diabetic patients. Peroneal artery was less frequent involved. He divided the arterial foot arch into the posterior and anterior arches and found that the posterior arterial foot arch was more often preserved than the anterior foot arch (1). Four years later (1993) two studies were published (2)(3), Ciavarella A. and his colleagues also found that diabetics had severely involved tibioperoneal segment but disagreed with the
suggestion that diabetics had a relatively spared arterial foot arch (2). Hilfiker M. and his colleagues (3) found no statistically significant difference between diabetics and non-diabetic patients concerning the pattern and distribution of PAD as well as involvement of the arterial foot arch. Some studies noted that non-diabetic patients had more pronounced involvement of aortoiliac and femoropopliteal segments than diabetic patients (2).

**Pattern and distribution of PAD in DM patients according to their risk factor combinations**

Towards the end of the century the questions addressed by researchers were shifting from those of pattern and distribution of arterial disease in diabetic versus non-diabetic patients to those of pattern and distribution according to risk factor profile. Among the first publications to address this question were Karacagil S. and colleagues 1996(5): looking at normotensive vs hypertensive in diabetics and non-diabetics. The occlusion rate was higher in diabetic patients (both hypertensives and normotensives) relative to non-diabetics (hypertensives 77% vs 56% ; normotensives 73% vs 51% respectively). Concerning the arterial foot arch they found that the incidence of having both foot arches intact was significantly higher in nondiabetic patients with hypertension. The conclusion therefore was that hypertension does not seem to contribute to the extent and severity of lower leg and foot vessel involvement. N. Diehm and his colleagues in 2006(10) investigated the risk factor profile association with pattern and distribution of PAD in 2659 patients. The following were their findings:

- **Iliac disease** was associated with younger age, cigarette smoking and male gender.

- **Infragenicular disease** was associated with diabetes mellitus, older age, and male gender,

- Hypercholesterolemia was less prevalent in patients with lesions below the knee.

- Hypertension was associated with no distinct pattern.

Lack of standardized angiographic reporting schemes particularly for infragenicular disease was a major problem in comparing
results from different researchers. Some authors suggested methods of categorising disease severity (8) as a way of trying to address this problem.

Despite this, the dominant notion in the literature was that of diabetic patient having a severe involvement of distal arterial segment than their non-diabetic counterparts.

**Arterial foot arch status in diabetic patients**

Recent studies investigated the impact of the quality of the arterial foot arch on various outcomes ranging for rate of wound healing rates, graft patency rates as well as amputation free survival(17)(18). The general impression is that the quality of the arterial foot arch has a positive impact on the wound healing rate but does not affect the graft patency rate or the amputation free survival (17)(18). Direct vs indirect pedal angiosome revascularization in patients with critical limb ischaemia is an area of active research (19)(22)(23)(24)(26)(27)(28)(29)(30)(31). A recent meta-analysis and systematic review (2014) of nine studies concluded that when feasible direct foot angiosome revascularization may improve salvage and wound healing rates when compared with the indirect foot angiosome revascularization. .

It remains a task of future research work to better model and design their studies in order to provide good evidence in answering these questions.

*Very little if any research work concerning this topics has been carried out in Africa.*

**Future perspective**

While admitting that it is impossible to completely avoiding confounding factors when addressing this topic, it is relevant to interrogate the nature of associations observed when stratifying patients according to patient-specific variables. It is the writer’s opinion that this approach would guide us in focusing resource usage in effectively managing this heterogeneous group of patients.
13. METHODS

This is a one year prospective descriptive study (January 2014 to December 2014) carried out at Groote Schuur Hospital, Vascular Department. An informed consent was completed by the patient to be included in the study. (see appendix A: copy of consent form)

13.1. Inclusions Criteria

Included in this study are:

- All diabetic patients ≥18 years of age with critical limb ischemia (Rutherford clinical category 4 – 6)
- Patients who had pre and post-intervention vascular imaging.

13.2. Method of data collection

Data was collected into a Microsoft Access database which is password protected and stored on a dedicated computer.

To ensure data consistency our database is designed with the following functionalities

- Calendar date pickups
- Drop down menus with either multiple select or single select options
- Fixed data types

(See Appendix C for the database snapshot.)

13.3. Patency level recording for aorto-iliac to tibioperoneal arterial segments:

All 12 main arteries on the symptomatic side from the infra-renal aorta to the crural arteries (Fig 1.01) had their patency levels graded and recorded using a very simple grading system (Fig 1.02).
Patency level Grading System for aorto-iliac to tibioperoneal arterial segments

**Category 1: Widely patent** (Angiographic image with clean pristine edges)

**Category 2: Diffusely diseased but patent** (Shaggy edges but no obvious stenosis)

**Category 3: Haemodynamically insignificant occlusive lesions** (Areas with <50% stenosis)

**Category 4: Haemodynamically significant occlusive lesions** (Areas with ≥ 50% stenosis)

**Category 5: Arterial occlusion** (segmental or complete)

*Fig 1.02* shows imaging representations of the above patency grading system
13.4. Arterial Foot Arch Classification

The arterial foot arch status was assessed on pre-interventional digital subtraction angiograms (DSA) and where feasible, post-interventional DSA after the inflow into the arch has been improved. The arterial foot arch is formed when the lateral plantar artery runs across the bases of the metatarsal bones and anastomoses with the dorsalis pedis artery through the deep plantar artery.

The arch status was assessed as follows:
- **Complete**: The anastomosis between the lateral plantar and the dorsalis pedis is intact filling the metatarsal and digital arteries.
- **Incomplete**: The anastomosis between the two arteries is not observed.
- **Absent**: No visualized foot arch.

The findings of the two variables (patency level of arterial segments and the arterial foot arch status) were then each stratified according to:
1. Gender
2. Age groups (<40 years; 40-54 years and ≥55 years)
3. Risk factor combinations of patients:
   - Group 1 = (DM, HPT, Dyslipidemia);
   - Group 2 = (DM, HPT, dyslipidemia, exsmoker);
   - Group 3 = (DM, HPT, dyslipidemia, smoker).

The above three risk combination groups formed the majority of our study group (79%).

13.5. Statistics

The calculated minimum sample size of 63 limbs (756 patency levels (63x12)) was needed to achieve a power of 86% to detect a difference of 0.1900 (19%) with a target significance level of 0.0500 (using PASS 11 software). The equality of distribution of categories was analyzed using the One sample Chi-square test (SPSS 21) with our Null hypothesis (N0) assuming that categories occur with equal proportions.

14. Results

Seventy six patients enrolled into this study and five were excluded from the study for not having any vascular imaging (poor candidates for revascularization). Therefore seventy one patients (71 limbs) were analyzed:
- 38/71 females
- 33/71 males.

**The age group composition:**
- Only one patient was younger than 40 years (female).
- 16 patients were 40-55 years.
- 54 (76%) patients were ≥ 55 years.

**Risk factor profile:** Three risk factor combinations dominated (comprising 79% of our patients):
- Group 1 (DM, HPT, Dyslipidemia);
- Group 2 (DM, HPT, dyslipidemia, ex-smoker)
- Group 3 (HPT, dyslipidemia, smoking)

The remaining 21% constituted variable risk factor combinations which were too small to assign to a group for statistical analysis.

**14.1. AORTO-ILIAC TO TIBIOPERONEAL SEGMENT PATENCY LEVEL ANALYSIS**

**14.1.1. Pattern and distribution of PAD in all diabetic patients**

Table 1.d shows the total number of patency categories recorded. There were 8 aorto-iliac segments which were not imaged which translates to 32 un-imaged aortoiliac arteries (4x8 = 32 arteries). Therefore the total number of imaged arteries is (852-32 = 820).

<table>
<thead>
<tr>
<th>PATENCY GRADES</th>
<th>TOTALS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category 1</td>
<td>117</td>
</tr>
<tr>
<td>Category 2</td>
<td>428</td>
</tr>
<tr>
<td>Category 3</td>
<td>52</td>
</tr>
<tr>
<td>Category 4</td>
<td>76</td>
</tr>
<tr>
<td>Category 5</td>
<td>147</td>
</tr>
<tr>
<td>Unimaged arteries</td>
<td>32</td>
</tr>
<tr>
<td>TOTAL</td>
<td>852</td>
</tr>
</tbody>
</table>

*Table 1.d* Total number of arteries in each patency category

The distribution of this patency levels across the 12 arteries as well as the three arterial segments is shown on Table 1.e & 1.f and Fig 1.03 & 1.04. The Null hypothesis assumes that the distribution of each patency category is equal across the 3 arterial segments (aorto-iliac, femoropopliteal, and tibioperoneal segments). It is important to note that there are 4 arteries graded at each segment.

It becomes evident on Fig 1.04 that the severity of disease increases from proximal arterial segments (aorto-iliac segment) to distal arterial segments (tibioperoneal segment). The reverse is true for the less severe patency categories (category 1 & 2) showing that the proximal segments are more patent than distal segments. Category 3 is equally distributed (P =0.779, therefore
retaining the null hypothesis). The distal predominance of category 4 and 5 is statistically significant (P < 0.001). The proximal predominance of category 1 and 2 is also statistically significant (P < 0.001 and P = 0.05 respectively). Significance levels are shown in Table 1.c as asymptotic significance level of chi square test.

Table 1.e (above) Total recorded patency categories in each artery
Table 1.f (below) Total recorded patency categories in arterial segment
14.1.2. Age group stratified pattern and distribution of PAD

Only one patient was younger than 40 years (Fig1.05). Table 1.g shows total number of all patency categories per age group. There are 12 patency categories recorded for the one patient <40 years age; 188 patency categories for 40-54 age group and 620 patency categories for ≥55 years age group (Table 1.g). Fig 1.06 shows the distribution of this patency categories across the arterial segments in a bar chart form. There are relatively more category 4 and 5 patency levels found in the tibioperoneal segment. The statistical significance for this disproportionate distribution is P <0.001 & P = 0.003 respectively for ≥55 age group; P = 0.013 & P = 0.019 respectively for age group of 40-54 (Table 1.h).
Fig 1.06 Age group stratified patency categories

Table 1.e Age group stratified arterial segments patency categories with statistical significance of proportions

Table 1.h Age group stratified segment patency categories with significance level of proportions
14.1.3. Gender stratified pattern and distribution of PAD

38 females and 33 males were analyzed (Fig 1.07). Table 1.f shows all patency levels recorded for males and females, with 388 grades recorded for males and 432 recorded for females. Table1.j and Fig 1.08 show the distribution of these patency levels across the three arterial segments. The frequency of category 5 and category 4 increase from proximal to distal segments with predominance in tibioperoneal segments (P <0.001 & p = 0.001 respectively for females; P < 0.001 & P=0.026 respectively for males). Likewise the widely patent arteries (category 1) are predominantly found in the aorto-iliac segment (P <0.001 for both females and males). It is worth noting that though there are more females than males in this study, females had no category 5 lesions in the aortoiliac segments compared to males who had 6 category 5 lesions in this segment.
14.1.4. Risk factor stratified pattern and distribution of PAD

Three risk factor combinations form the bulk of our patients. **Group 1** (DM, HPT, Dyslipidemia); **Group 2** (DM, HPT, dyslipidemia, exsmoker) and **Group 3** (DM, HPT, dyslipidemia, smoker). These risk factor combinations account for 79% of our patients (labelled common combinations in Fig 1.09). The remaining 21% is almost
equally divided amongst the other 4 risk factor combinations (Fig 1.09).

A total of 656 patency categories (115+60+42+354+85 = 656) were described for groups 1, 2 and 3 (Table 1.h). Table 1.i shows the distribution of patency levels across the arterial segments for the three common risk factor combinations. Asymptotic significance levels (P value equivalence) are shown in table 1.l. Group 1 and group 2 displayed the classic observation of worse disease in the distal arterial segment (Fig 1.11). For these two risk factor combinations, category 5 lesions predominate the tibioperoneal segment (P<0.001 for both risk factor combinations). In contrast group 3 have significantly unequal distribution of category 5 (occlusions) patency levels (P<0.001) but with more occlusions in the femoropopliteal segment than in the tibioperoneal segment. The rest of other grades of patency level in group 3 are almost equally distributed (P > 0.05).

Fig 1.10 shows the 4 risk factor combination that constituted the minority of our patients as a frequency bar chart of patency levels for each of them.
Table 1.k Frequency table for each patency category per risk factor combination group

<table>
<thead>
<tr>
<th>Risk Factor Profile</th>
<th>Category 1</th>
<th>Category 2</th>
<th>Category 3</th>
<th>Category 4</th>
<th>Category 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>DM, DYSL, HPT</td>
<td>45</td>
<td>29</td>
<td>12</td>
<td>127</td>
<td>39</td>
</tr>
<tr>
<td>DM, DYSL, HPT, SMOK</td>
<td>35</td>
<td>19</td>
<td>16</td>
<td>136</td>
<td>26</td>
</tr>
<tr>
<td>DM, DYSL, HPT, EXSMOK</td>
<td>35</td>
<td>12</td>
<td>16</td>
<td>91</td>
<td>20</td>
</tr>
<tr>
<td>TOTAL</td>
<td>115</td>
<td>60</td>
<td>42</td>
<td>354</td>
<td>85</td>
</tr>
</tbody>
</table>

Table 1.j Risk factor stratified patency category frequency table

<table>
<thead>
<tr>
<th>RF Profile</th>
<th>Arterial Seg</th>
<th>Category 1</th>
<th>Category 2</th>
<th>Category 3</th>
<th>Category 4</th>
<th>Category 5</th>
<th>Category 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>DM, DYSL, HPT</td>
<td>AORTO-IJAC</td>
<td>1</td>
<td>3</td>
<td>5</td>
<td>49</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>DM, DYSL, HPT</td>
<td>FEM-POP SEG</td>
<td>10</td>
<td>10</td>
<td>5</td>
<td>47</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>DM, DYSL, HPT</td>
<td>TIBIO-PERONE</td>
<td>34</td>
<td>16</td>
<td>2</td>
<td>31</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>ASYMPTOTIC SIGN</td>
<td>0.009</td>
<td>0.013</td>
<td>0.472</td>
<td>0.100</td>
<td>0.009</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DM, DYSL, HPT, SMOK</td>
<td>AORTO-IJAC</td>
<td>0</td>
<td>2</td>
<td>4</td>
<td>52</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>DM, DYSL, HPT, SMOK</td>
<td>FEM-POP SEG</td>
<td>19</td>
<td>8</td>
<td>5</td>
<td>42</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>DM, DYSL, HPT, SMOK</td>
<td>TIBIO-PERONE</td>
<td>16</td>
<td>9</td>
<td>7</td>
<td>42</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>ASYMPTOTIC SIGN</td>
<td>0.000</td>
<td>0.104</td>
<td>0.646</td>
<td>0.544</td>
<td>0.005</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DM, DYSL, EXSM, HPT</td>
<td>AORTO-IJAC</td>
<td>2</td>
<td>1</td>
<td>8</td>
<td>34</td>
<td>7</td>
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</tr>
<tr>
<td>DM, DYSL, EXSM, HPT</td>
<td>FEM-POP SEG</td>
<td>11</td>
<td>5</td>
<td>1</td>
<td>32</td>
<td>11</td>
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</tr>
<tr>
<td>DM, DYSL, EXSM, HPT</td>
<td>TIBIO-PERONE</td>
<td>22</td>
<td>6</td>
<td>5</td>
<td>25</td>
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<tr>
<td>ASYMPTOTIC SIGN</td>
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<td>0.646</td>
<td>0.544</td>
<td>0.005</td>
<td></td>
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</tbody>
</table>
Fig 1.09 Frequency bar chart for risk factor combinations

Fig 1.10 Risk factor stratified segment patency levels for the small proportion risk

Fig 1.11 Risk factor stratified segment patency levels for the dominant groups
14.2. **Arterial Foot Arch Status Analysis:**

The arterial foot arch status was assessed on pre-interventional digital subtraction angiograms (DSA) and where feasible, post-interventional DSA after the inflow into the arch has been improved. The arterial arch is formed when the lateral plantar artery runs across the bases of the metatarsal bones and anastomosis with the dorsalis pedis artery through the deep plantar artery. (Figure 1.12) shows a schema of the arterial foot arch.

The arch status was assessed as follows:

- **Complete:** the anastomosis between the lateral plantar and the dorsalis pedis is intact filling the metatarsal and digital arteries
- **Incomplete:** the anastomosis between the two arteries is not observed
- **Absent:** No visualized foot arch

14.2.1. **All diabetic patients:**

Fig 1.12 shows the frequency of arterial foot arch patency levels

- 10 ➔ absent (occluded);
- 28 ➔ incomplete;
- 31 ➔ complete;
  - 2 ➔ poor imaging of the foot arch with lots of motion artifacts (unclassified).

Disproportionate distribution among the three arterial foot arch patency levels was significant (P = 0.004). Although the majority of patients had a complete arch, the difference between numbers
of patients with complete vs incomplete arch was only 3. On the other hand there were significantly fewer patients with absent foot arch (almost three times smaller than the other groups).

**14.2.2. Gender stratification of arch status:** On stratifying the above observation according to gender, it becomes clear that a good proportion of females {22/38 (58%) females} vs [9/33 (27%) males} have a complete arch. Relatively fewer females {4/38(11%)} had absent arch vs {6/33(18%)} in males. The majority of males had an incomplete foot arch {17/33(58%)}. For both females and males there was disproportionate distribution between the categories of the arch status categories (P = 0.004 females and P = 0.048 males) *Table 1.m.* Therefore this disproportionate distribution cannot be explained by chance alone.

![Fig 1.13 Arch status frequency bar chart](image)

*Table 1.m Gender stratified arch status frequency*
14.2.3. **Age group stratified arch status**: Most of our patients were ≥55 years of age and their distribution among the arch status categories was significantly disproportionate ($P = 0.028$) with more patients having complete foot arches (23/54) followed by incomplete foot arches (21/54). Only 8/54 patients in these age group had an absent arterial foot arch. There were 16 patients in the 40-54 years age group. Only 2/16 had absent foot arches and the remaining (14) were equally divided between the complete and incomplete foot arch categories. Only one patient was younger than the 40 years and she had a complete foot arch.
14.2.4. Risk factor profile stratified arch status

Three risk factor combinations dominated. 79% of our patients belonged to one of the following risk factor profiles:

1. DM, HPT, Dyslipidemia (Group 1)
2. DM, HPT, Dyslipidemia, Exsmoker (Group 2)
3. DM, HPT, Dyslipidemia, Smoker (Group 3)

Group 2 (DM, HPT, Dyslipidemia, Ex-smoker) had predominantly complete foot arches 9/13. The remaining 4 patients were equally distributed between incomplete and absent foot arches. For Group 3 (DM, HPT, Dyslipidemia, Smoker) and Group 1 (DM, HPT, Dyslipidemia) proportions in each foot arch status category were almost the same with slight predominance of incomplete foot arch, followed by complete foot arch as shown in the Table 1.n and Figure 1.16. These unequal distribution within the risk factor combinations were statistically significant (P<0.05) Table 1.n.
15. DISCUSSION

Research work concerning this topic took off in the 1980s (1) (2) with the advent of DSA. A number of studies supported the notion that diabetic patients with peripheral artery occlusive disease have severe involvement of tibioperoneal segment (1) (2) (11) (5) (10) (8) and relative sparing of the arterial foot arch (1). However, some studies disagreed with this notion of severe distal arterial segment involvement in diabetic patients (3) and the arterial foot arch sparing (3) (2).

Understanding the variability of pattern and distributions of PAD according to risk factor profile, gender, and age group would add further to our understanding of these observations.

15.1. Our study highlighted key findings which are worth mentioning:

In general, we found that diabetic patients have severe distal arterial segment involvement. Female diabetic patients have relatively less severe disease. Group 3 (DM, HPT, Dyslipidemia, Smoker) have a more severe involvement of the femoropopliteal arterial segment. This risk factor combination difference seems to explain the isolated peak in severe patency levels of SFA (occlusions and high grade occlusive disease) in Fig 1.03 when analyzing the distribution of patency levels artery by artery. Interestingly, a group with the same risk factor combinations except that they were exsmoker – group 3 (DM, HPT, Dyslipidemia, Exsmoker) – have less affliction of femoropopliteal segment. This seems to suggest that smoking increases the severity of arterial occlusive disease in the femoropopliteal segment or proximal segments. A study by N. Diehm, A. S.-D. (2006) (11) found that smoking had a higher relative risk ratio for severe affliction of the aorto-iliac segment.

In analyzing the arterial foot arch status, it turned out that female diabetic patients had significant relative arterial foot arch sparing while their male counterparts had a largely incomplete foot arch. A difficult question to answer would be what is it about females that protects them from more severe foot arch involvement. It is however a relevant question.
15.2. Shortcomings in our study:

We could not make statistically significant conclusions in all age group stratification analyses mainly because we lacked numbers in the younger age groups. The same problem arose when analysing risk factor profile stratification variables. A common problem highlighted in previous similar studies (8) is lack of a standardised reporting criteria for the infragenicular arterial lesions and foot arch assessment. This is a real problem particularly when trying to compare results during a literature review or when doing a retrospective study on reported infragenicular vascular imaging.

Future research perspectives:

Extending the period of study to beyond a year may help accumulate more patients to represent the less common categories like younger patients with critical limb ischaemia and rare risk factor combinations. Another option would be to run a multicenter study to gain more numbers to make statistically significant conclusions.
16. CONCLUSION

Diabetic patients in general have severe tibio-peroneal disease. This finding was consistent in both genders, in all patients aged 40 years and older and in Group 1 (DM, HPT, Dyslipidemia) (P<0.001) and group 2 (DM, HPT, dyslipidemia, exsmoker) (P<0.001). Group 3 (HPT, dyslipidemia, smoker) have a different distribution pattern, with more occlusions in the femoropopliteal segment (P<0.001) followed by tibioperoneal segment. This seems to suggest that smoking increases the severity of arterial occlusive disease in proximal segment.

Female diabetics tends to have a complete arterial foot arch (P=0.004) as opposed to male patients who have predominantly incomplete arch (P=0.048). The Group 2 patients have predominantly complete arterial foot arch while group 3 and group 1
References


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38. Leng GC. Incidence, natural history and cardiovascular events in symptomatic and asymptomatic peripheral arterial disease in the general population. *Int J Epidemiol*, 1172–81.


18. APPENDIX A

Copy of informed consent

UNIVERSITY
OF CAPE TOWN

Informed Consent

[This is a consent sheet that includes all of the required information that research participants are required to know before giving consent.]

Protocol Title: PATTERN AND DISTRIBUTION OF PERIPHERAL ARTERIAL DISEASE (PAD) IN DIABETIC PATIENTS WITH CRITICAL LIMB ISCHEMIA (RUTHERFORD CLINICAL CATEGORY 4-6)

Please read this consent document carefully before you decide to participate in this study.

Purpose of the research study

- The aim of this study is to study the pattern and distribution of Peripheral arterial disease in diabetic patients with critical limb Ischemia Rutherford category 4 – 6 and to stratify the pattern and distribution according to their atherosclerosis risk factor profile and age group.
- Identify a wound related artery in each patient.

Who is conducting: The study is conducted by Dr. Mpapho Motsumi as his MMED research topic. Supervised by Dr. Nadraj Naidoo with the relevance of understanding the disease pattern and distribution in our population of patients.

What you will be asked to do in the study:

The following information will be needed from your Medical records and you during admission:

- Patient assigned a unique identifier (excluding name), age, sex, date of admission
- Comorbidities and atherosclerosis risk factors
- Access to Duplex and radiological imaging to describe: Pattern and distribution of disease on imaging modalities, disease related artery identification and arch status,

Therefore the data to be collected will be available on the medical records and on imaging modalities records. Few questions may have to be asked to fill in the gaps in the medical records e.g. the ulcer location description and comorbidities.

Time required: Most of the times all the information will be available on the medical records and on imaging modalities systems and no interview will be needed. In few cases of missing information, after consent explanation less than 5 minutes will be more than sufficient to get the information from you with your consent.

Access to Existing Records: We request permission to access medical records only for information stated above. You retain the right to refuse access to your medical records and your decision will be respected without compromising your medical management benefits.

Risks and Benefits: This is a low risk research, there is no invasive procedure beside regular investigative procedures that all patients are routinely subjected to for their workup. There is no tissue collection or interventions involved. The long-term benefit is better understanding of diabetic vasculopathy in our setting which would shape current understanding and management of diabetic vasculopathy.

Compensation: This research is a non-profit making research and no compensation is offered to the participants.

Confidentiality: Your information security is assured by capturing and storing data in a password protected database accessible only to the Principal Investigator – Dr. Mpapho Motsumi and his
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Supervisor Dr. N. Naidoo. The researchers will be vigilant to observe measures necessary for your information confidentiality. You will be given a unique identifier that is computer auto-generated and linked to your folder number under a password protected database file. When the study is completed and the data have been analyzed, the identifier – folder number link will be destroyed. Study findings will be presented only in summary form and your name will not be used in any report.

Voluntary participation: Participation is voluntary. Your participation in this study is completely voluntary. If you choose not to participate in this study, this will have no effect on the services or benefits you are currently receiving.

Right to withdraw from the study: You may choose to stop participating in the study at any time. This will have no effect on the services you receive.

Who to contact if you have questions about the study:
Faculty of Health Sciences Human Research Ethics Committee
Room E52-24 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6338 • Facsimile [021] 406 6411
Email: shurett.thomas@uct.ac.za
Website: www.health.uct.ac.za/research/humanethics

YOU WILL BE GIVEN A COPY OF THIS FORM WHETHER OR NOT YOU AGREE TO PARTICIPATE.

If you agree to participate in this study please sign below:

Agreement:
I have read the procedure described above. I voluntarily agree to participate in the research and I have received a copy of this description.

Name (Printed) ____________________________
Signature: ________________________________
Date: ___________________________________ 

Principal Investigator: _____________________ Date: _________________
Signature: ________________________________
19. APPENDIX B

Copy of ethics approval
20. APPENDIX C

Data capture Database