Metabolic profile and post-operative outcomes in contemporary patients with peripheral arterial disease and critical limb ischaemia

By

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DECLARATION OF AUTHENTICITY

I, Dr Lily Wu, hereby declare that the work, on which this dissertation is based, is my own. I have fully and specifically acknowledged sources from which material has been adapted. Furthermore, the information contained within this document, was gathered and utilized specifically to fulfil the purposes and objectives of this study and has not been previously submitted to any other university for a higher degree.

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ABSTRACT

Metabolic profile and post-operative outcomes in contemporary patients with peripheral arterial disease and critical limb ischaemia- an observational prospective cohort study

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Background: Peripheral arterial disease (PAD) is an established occlusive disease of the peripheral arteries and is not uncommon in the elderly. Atherosclerosis accounts for 90% of the pathology. Only 15% of affected individuals become symptomatic. Most symptomatic individuals present with intermittent claudication (IC). Only a small proportion (1%) of affected individuals present with critical limb ischaemia (CLI). Revascularization aimed at limb salvage, and recovery of ambulation and independent living is the ultimate therapeutic option for the advanced form of PAD (CLI). Traditionally, the success of revascularization for CLI has been defined by graft patency rates and limb salvage rates. Functional outcomes such as ischaemic wound healing and recovery of ambulatory function for independent living have been the focus in more recent publications. However, these assessments do not consider the patients' pre-operative metabolic profile as a predictor of post-operative outcomes.

Purpose: The purpose of this study was to determine, in a prospective manner, the influence of pre-operative metabolic profile on post-operative outcomes in contemporary patients with peripheral arterial disease presenting with critical limb ischaemia at a tertiary hospital in South Africa.

Methods: All consecutive patients, ≥18 years with CLI admitted to the vascular unit at Groote Schuur Hospital over a two-year period (1st January, 2015 to 31st December, 2016) with reconstructable disease were recruited for the study. Written informed consent was obtained from all participants. Revascularization entailed either open surgical revascularization, endovascular interventions or both (hybrid procedures). Data was analyzed according to the clinical level of disease and the type of surgical intervention. Post-operative outcome measures were determined.

Primary endpoints (functional and technical outcomes)

- Ambulatory recovery at six months and one year
- Complete ischaemic wound healing at six months and one year
- Limb salvage rate at six months and one year

- Primary graft patency rate at six months and one year

Secondary endpoint

- The influence of pre-operative metabolic profile on the post-operative outcomes

The association between pre-operative metabolic profile and post-operative outcomes was determined by Pearson Chi-square statistical test and logistic regression model.

Results: A total of 73 consecutive patients were recruited for this study with a mean age of 58 ± 9 years (Range: 30 - 75 years). Seventeen patients (23.3%) had rest pain and 56 (76.7%) had tissue loss. Current smokers and previous smokers constituted 86% of the sample population with a male to female ratio of approximately 1:1. Our study population was generally overweight based on the BMI. There was high prevalence of abdominal obesity and high body fat for both males and females.
Recovery of ambulatory status was 69% and 67% at six months and one year follow-up respectively. The rate of ischaemic wound healing at six months and one year was 48.2% and 75.0% respectively. Surgical site sepsis was the most common local wound complication. Limb salvage rate was 78% and 79% at six months and one year respectively. Overall primary graft patency at six months was 69.0% but reduced to 60.0% at one year. Major amputation rate at one year was 21%. Most of the post-operative wound-related complications occurred among patients with diabetes. More diabetic patients had major amputations compared to non-diabetic patients (57.9% vs 42.1%). One year amputation-free survival (AFS) was 69.9%. There were no statistically significant associations between metabolic profile of patients and post-operative clinical outcomes.

Conclusion: Demographics, co-morbidities, and procedural details of our study population, reflected a relatively younger population with CLI. The profile of this contemporary vascular surgery patients is that of overweight, high abdominal obesity, and high prevalence of smoking among both gender. The technical and functional outcomes observed in this study are consistent with available western literature. Diabetes was associated with prolonged ischaemic wound healing, higher risk of major amputation and local wound complications. A statistically significant association was not found between patients' metabolic profile and post-operative outcome but this could be due to the small sample size and short follow up period.

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Above all, I thank God for making this possible.

DEDICATION

To my dear husband (Charles) and children (Jason and Joshua), your love and support keeps me going. May God, bless you for all the sacrifices you made.

METABOLIC PROFILE AND POST-OPERATIVE OUTCOMES IN CONTEMPORARY PATIENTS WITH PERIPHERAL ARTERIAL DISEASE AND CRITICAL LIMB ISCHAEMIA

By

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TABLE OF CONTENTS

LIST OF TABLES AND FIGURES

Chapter 1

Chapter 2:

TABLES

FIGURES

ABBREVIATIONS

ABI	Ankle brachial pressure index
AI disease	Aorto-iliac disease
AKA	Above knee amputation
BKA	Below knee amputation
BMI	Body mass index
CAD	Coronary artery disease
CLI	Critical limb ischaemia
CTA	Computed Tomography Angiogram
CVD	Cardiovascular disease
DSA	Diagnostic peripheral angiogram
DUS	Duplex ultrasound
Fem-pop disease	Femoro-popliteal disease
Hb	Haemoglobin
IBS	Infra-inguinal bypass surgery
IC	Intermittent claudication
INR	International normalized ratio
IQR	Interquartile range
MINORS	Methodological Index for Non-Randomized Studies
MUAC	Mid-upper arm circumference
PAD	Peripheral arterial disease
PTA	Percutaneous trans-luminal angioplasty
PTFE	Polytetrafluoroethylene
RSVG	Reverse saphenous vein graft
SIB	Supra-inguinal bypass surgery
SMA	Supra-malleolar amputation
TMA	Trans-metatarsal amputation
TP disease	Tibio-peroneal disease
TSFT	Triceps skin fold thickness
WHR	Waist-hip circumference ratio

Chapter 1

Metabolic profile and post-operative outcomes in contemporary patients with peripheral arterial disease and critical limb ischaemia: A Systematic Review and Meta-analysis.

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BACKGROUND

Peripheral arterial disease is defined, anatomico-pathologically, as established chronic occlusive disease of the peripheral arteries with specific reference to the lower limbs. Peripheral arterial disease (PAD), from a community screening perspective, is defined as an ankle-brachial pressure index (ABI) of less than 0.9 (1), (2), (3).

Diagnosing PAD using ABI	Clinical significance
>1.4	Non-compressible vessels; may indicate vessel calcification
1.0-1.4	Normal
0.91-0.99	Borderline
<0.9	PAD

Atherosclerosis forms the pathological basis for approximately 90% of PAD. In the western literature, PAD is generally synonymous with atherosclerotic PAD. Peripheral arterial disease usually co-exists with atherosclerosis in other vascular beds. Consequently patients with PAD are at an increased risk of stroke, myocardial infarction and cardiovascular death (4). A low ABI is a potent surrogate marker for future cerebrovascular and cardiovascular events (5), (6), (7).

The prevalence of PAD varies widely and increases dramatically with increasing age (1), (2), (3). It ranges from 3% to10% generally, but increases to 20% in persons over 70 years (8). There are also some racial differences in the prevalence of PAD. It disproportionately affects blacks (3). Age-adjusted estimates showed that non-Hispanic blacks and Mexican-Americans had a higher prevalence of PAD than non-Hispanic Whites (19.2%, and 15.6% respectively) (3). Dominant risk factors for PAD include advancing age, smoking, diabetes mellitus, hypertension and hyperlipidaemia (1), (2), (3), (4).

The vast majority of affected individuals with established PAD are asymptomatic. It is estimated that for every symptomatic individual with PAD, 3-4 individuals with PAD are asymptomatic. Being asymptomatic does not protect individuals with PAD against cardiovascular and cerebrovascular events, and vascular death. These patients have a reduced life expectancy compared to individuals without PAD. It has been shown that effective risk factor control is associated with a reduction in cardiovascular events and mortality in individuals with peripheral arterial disease (6), (9). The principal complimentary aims in the treatment of PAD is to reduce the risk of cardiovascular events such as myocardial infarction and stroke as well as to provide symptomatic relief. Comprehensive management of PAD emphasizes optimum medical treatment (OMT) in all patients with PAD.

Lifestyle modification includes weight loss in overweight individuals, exercise therapy (preferably supervised exercise programmes) and smoking cessation strategies (4), (10), (11). Smoking cessation lowers the risk of PAD but not to the same degree as lifetime non-smokers (12), (10), (13). Optimum medical treatment is informed currently by evidence-based pharmacotherapy. Currently antiplatelet therapy and lipid-lowering strategies emphasizing statins constitute the medical standard of care in patients with established PAD. Antiplatelet therapy has been proven to be effective in secondary prevention of cardiovascular events (14). Target blood pressure control to <140/90 mmHg in patients with documented PAD, and <130/80 mmHg in patients with other atherosclerotic risk factors like diabetes or renal insufficiency is recommended. Good plasma glucose control (HbA1c <7%, current American Diabetes Association guidelines on treatment goal for all patients with DM) in individuals with diabetes is also desirable (4), (15), (16), (17). Adherence to these guidelines leads to a significant reduction in major adverse cardiovascular events as well as fewer major adverse limb events (18).

Revascularization strategies are generally reserved for the treatment of the advanced form of PAD, viz, severe life-style limiting, medically refractory claudication, and critical limb ischaemia (CLI). Revascularization strategies include endovascular interventions, open surgical vascular procedures or both (hybrid procedures). Generally open vascular surgical intervention for PAD is associated with not insignificant post-operative morbidity and mortality. Specific early post-operative complications include local wound complications (haemorrhage, hematoma, wound sepsis, etc.) early graft infection and early graft thrombosis. Late complications include late graft occlusion, late graft sepsis, anastomotic aneurysms, etc. Wound-related complications may necessitate re-admission and further surgical procedures. Thus, patients with CLI sometimes experience protracted post-operative recovery accompanied by multiple re-operations and hospital admissions. In some cases, the post-operative wound complications result in major amputations which impacts negatively on quality of life (social isolation and depression) (4). Productivity in terms of work and income is also adversely affected. Caring for such physically disabled individuals by family and caregivers is also a challenge. Many of the individuals who ultimately undergo major amputations are in some cases financially supported by Social Welfare through monthly stipends. This adds further burden on the already limited economic resources available in developing countries. The traditional measures that have historically been used to determine the success of operative interventions are limb salvage and graft patency. Functional outcomes such as ambulatory recovery and ischaemic wound healing however have been shown in recent reports to be better outcome measures to assess clinical success of operative interventions for CLI, (19), (20), (21), (22), (23).

Factors that may influence post-operative outcomes may include pre-operative metabolic profile, risk factors for atherosclerosis, clinical level of disease, concurrent co-morbidities, the type of revascularization procedure, surgical expertise and duration of surgery. In patients with CLI and tissue loss, ischaemic wound healing is confounded by the extent of revascularization, the presence of diabetes

mellitus, sepsis and metabolic profile. Optimal metabolic support is required for adequate recovery of patients following any surgical operation including vascular interventions. Such optimal metabolic support limits catabolism, promotes wound healing, and mobilizes appropriate defense mechanisms against infection (24). The metabolic profile refers to an individual's physical/physiological wellbeing assessed by anthropometric measurements and haematological/biochemical evaluation. It is a measure of one's immune competence to withstand adverse events like trauma, major surgery and infections. It is also a measure of the body's wound healing capacity. Patients with metabolic syndrome are known to have increased insulin resistance and to be at increased risk for adverse cardiovascular events (25). Nutritional status of patients has been proven to influence surgical outcome in terms of post-operative complications (26). Anthropometric measurements, haematological and biochemical tests are proven methods of evaluation of the metabolic profile (27), (28). Anthropometric measurements such as mid-upper arm circumference (MUAC) provides a measure of muscle mass while triceps skin fold thickness (TSFT) provides an excellent index of body fat. These methods are more accurate in their assessment of protein-based nutritional status (24). Serum transport proteins (i.e. albumin, pre-albumin, and transferrin) are good indicators of visceral protein mass. Pre-albumin and transferrin levels are highly sensitive indicators of nutritional status. However, their levels change erratically during stress and illness. In addition to this limitation, the cost of determination of pre-albumin and transferrin levels are very high making them universally unacceptable tools for routine clinical use (24). Albumin is synthesized in the liver and has a half-life of 18 to 21 days. Total albumin varies from 3 to 4g/kg in women and 4 to 5g/kg in men. Of these three blood tests, serum albumin is the most useful measure of nutritional status (29), (30). Albumin level of < 3.5 g/dl is associated with increased morbidity in intensive care unit and other hospitalized patients (31). Malnutrition has been linked to increased length of hospital stay, increased costs of treatment, and higher rates of complications (32). In surgical patients, poor pre-operative nutritional status has been associated with high post-operative morbidity and mortality (33). Post-operative complications and deaths were found to be more likely if patients were malnourished (34). Malnourished adult patients are usually underweight with a body mass index (BMI) ≤ 18.5. A low BMI < 15 is associated with significant increase in post-operative morbidity (35), (36). BMI <18.5 is associated with a longer stay in intensive care unit, increased risk of post-operative complications and higher re-admission rates (36).

Conversely, being overweight ($25 <$BMI≤ 29.9) or obese (BMI ≥ 30) also influence surgical outcome with respect to morbidity (wound-related complications, length of hospital stay, deep vein thrombosis, etc.) and mortality (34), (37). In a study by Lemaignen et al. to evaluate the risk factors for surgical site infection after cardiac surgery, advancing age, obesity and diabetes mellitus were among the risk factors identified (38). In another study on the effect of BMI on the 30-day morbidity and mortality involving vascular surgery patients, obesity was associated with the highest morbidity (34). Nam et al. also reported a higher risk of wound complications with infra-inguinal vein bypass graft in obese patients

(39). In patients with thigh arterio-venous shunts, obesity was associated with increased access failure and significant re-intervention rate(40).

However, Nicholson et al., reported that obesity was not a risk factor for complications following vascular reconstructive surgery (37). Gurm et al, similarly, found no association between BMI and early outcomes following carotid angioplasty and stenting (CAS) (41). Chang et al., also did not observe any significant association between obesity and wound infection rates after lower extremity revascularizations (42). Thus, the data available currently is contradictory with respect to the effect of patients' metabolic profile on post-operative outcomes. The paucity of literature locally regarding this subject necessitates a study to interrogate the issue. Besides, the conflicting report as shown above further strengthens the need for this study.

ABSTRACT

Background: Peripheral arterial disease (PAD) is an established occlusive disease of peripheral arteries; particularly the lower limbs and is not uncommon in the elderly (1). Only a small proportion of individuals with PAD (15%) are symptomatic. An even smaller proportion (1%) present with CLI (43). The major risk factors for atherosclerotic PAD include advancing age > 55 years, smoking, diabetes mellitus, hypertension and hypercholesterolemia. PAD is an independent risk factor for cardiac events (44). Hence individuals with PAD generally have shorter lifespan relative to an age matched cohort without PAD. The present review evaluated the current literature on surgical outcomes of patients with CLI, and assessed any associated pre-operative predictors of post-operative outcomes.

Methods: PubMed/Medline, Google scholar and Cochrane databases were systematically searched for relevant English-language articles published between January 2007 and December 2016 (10 years period) using the terms "peripheral arterial disease AND critical limb ischaemia," "peripheral arterial disease AND post-operative outcome," etc. Selected articles were screened first by title and abstract. Full-text articles were subsequently screened using our inclusion and exclusion criteria and quality ratings were performed with the MINORS score. The primary endpoint was a composite of post-operative technical and functional outcome measures. The secondary endpoint was identification of predictors of post-operative outcomes.

Results: A total of 2,114 articles were identified. Only six articles met our eligibility criteria and were deemed suitable for analysis. Ambulatory recovery was >70% at six months, and 86.7%, 73.0% and 70.6% at one year, three years and five years respectively. Local wound complications recorded were between 12% and 24%. In some studies >50% of the ischaemic wounds took more than three months to heal. In one study the wound healing rate at six months and one year was 42% and 75% respectively. Reported limb salvage rates were >90% at six months, >70% at one year and 70.0-90.0% at five years. Primary graft patency rate at one year ranged from 63% and 76.6%. Gangrene, diabetes and impaired pre-operative ambulatory function are associated with more wound complications, low limb salvage, reduced graft patency and poor functional outcome (19, (21), (45), (46), (47).

Conclusion: Multiple factors predicted post-operative outcomes, but none of the studies considered patients' pre-operative metabolic profile. Pre-operative ambulatory status was the most important predictor of post-operative ambulatory recovery. Diabetes mellitus was an important risk factor for prolonged wound healing, local wound complications and major amputation.

Keywords:
Peripheral arterial disease, critical limb ischaemia, post-operative outcomes

INTRODUCTION

The prevalence of peripheral arterial disease varies widely and increases with increasing age (1), (3). In the National health and nutrition examination survey (NHANES), the overall prevalence was reported as 4.3%. For people between 40 and 50 years, the prevalence was only 0.9% but for those older than 70 years, the prevalence was 14.5% (1). Only a small proportion of individuals with PAD (about 15%) are symptomatic. An even smaller proportion (1%) present with CLI (43). The Reduction in Atherothrombosis for Continued Health Registry (REACH) study reported that asymptomatic individuals with PAD have a prognosis almost as poor as those with symptomatic disease (48). Peripheral arterial disease is an independent risk factor for cardiac events (44). Hence individuals with PAD generally have shorter life expectancy relative to an age matched cohort without PAD. The cardiovascular event rate in individuals with PAD is considerably higher compared to patients with cerebrovascular disease or even coronary artery disease (6). The risk of PAD among current smokers is 4 times higher than non-smokers with a dose-related association clearly established. Diabetes mellitus is rapidly emerging as potent risk factor for atherosclerotic PAD. For every 1% drop in HbA1c, there is a corresponding 28% reduction in risk of PAD. In hypertensive patients, for every 10 mmHg drop in systolic blood pressure there is an associated 10% risk reduction in cardiovascular mortality (8).
The present review is on the current report on surgical outcomes of patients with CLI and predictors of post-operative outcomes.

METHODS

Literature search: PubMed/Medline, Google scholar and Cochrane databases were systematically searched for relevant English-language articles published between January 2007 and December 2016 (10-year period) using the terms “peripheral arterial disease” AND “critical limb ischaemia,” “peripheral arterial disease” AND “post-operative outcome,” and “critical limb ischaemia” AND “post-operative outcomes or complications”. Selected articles were screened first by title and abstract, and selection was based on relevance. Full-text articles were subsequently screened using our inclusion and exclusion criteria and quality ratings performed with the MINORS score (49).

Methodological items for non-randomized studies	Score†
1. **A clearly stated aim:** the question addressed should be precise and relevant in the light of available literature 2. **Inclusion of consecutive patients**: all patients potentially fit for inclusion (satisfying the criteria for inclusion) have been included in the study during the study period (no exclusion or details about the reasons for exclusion) 3. **Prospective collection of data**: data were collected according to a protocol established before the beginning of the study 4. **Endpoints appropriate to the aim of the study**: unambiguous explanation of the criteria used to evaluate the main outcome which should be in accordance with the question addressed by the study. Also, the endpoints should be assessed on an intention-to-treat basis. 5. **Unbiased assessment of the study endpoint**: blind evaluation of objective endpoints and double-blind evaluation of subjective endpoints. Otherwise the reasons for not blinding should be stated 6. **Follow-up period appropriate to the aim of the study**: the follow-up should be sufficiently long to allow the assessment of the main endpoint and possible adverse events 7. **Loss to follow up less than 5%**: all patients should be included in the follow up. Otherwise, the proportion lost to follow up should not exceed the proportion experiencing the major endpoint 8. **Prospective calculation of the study size**: information of the size of detectable difference of interest with a calculation of 95% confidence interval, according to the expected incidence of the outcome event, and information about the level for statistical significance and estimates of power when comparing the outcomes *Additional criteria in the case of comparative study* 9. **An adequate control group**: having a gold standard diagnostic test or therapeutic intervention recognized as the optimal intervention according to the available published data 10. **Contemporary groups**: control and studied group should be managed during the same time period (no historical comparison) 11. **Baseline equivalence of groups**: the groups should be similar regarding the criteria other than the studied endpoints. Absence of confounding factors that could bias the interpretation of the results 12. **Adequate statistical analyses**: whether the statistics were in accordance with the type of study with calculation of confidence intervals or relative risk	

†The items are scored 0 (not reported), 1 (reported but inadequate) or 2 (reported and adequate). The global ideal score being 16 for non-comparative studies and 24 for comparative studies.

Fig 1: MINORS Score(49)

Inclusion criteria: All published articles involving patients' metabolic and or risk factor profile and at least three post-operative outcome measures (technical, functional or both)

Exclusion criteria: Reviews, case reports, abstracts only, meta-analysis, articles that require payment to access, non-English articles and duplicate articles.

Primary endpoint:

- Technical and/or functional post-operative outcomes

Secondary endpoint:

- Predictors of post-operative outcomes

Validity assessment: Article screening, selection and data extraction were done by two reviewers independently to minimise bias. Identified relevant titles were selected as an initial step. All abstracts were read, and articles with clearly stated objectives of evaluation of predictors of post-operative outcomes or complications of surgical treatment of CLI were chosen. Using our eligible criteria, selected full articles were read, and selection made based on the presence of at least three of the outcome measures as defined in the reporting standards of revascularization for CLI (technical outcome measures) and/or functional outcomes or both. All related publications/electronic links of the selected articles were downloaded and the references perused to generate any further relevant publications. The quality of the selected articles was assessed using the Methodological Index for Non-Randomized

Studies (MINORS) quality score, with a maximum score of 16 for non-comparative studies and 24 for comparative studies (49).

Table 1: MINORS Score (6 Best performing Studies)

MINORS Score	Study Number (see KEY)					
	1	2	3	4	5	6
A clearly stated aim	2	2	2	2	2	2
Inclusion of consecutive patients	2	2	2	2	2	2
Prospective collection of data	0	0	2	0	0	0
Endpoints appropriate to the aim of the study	2	2	2	2	2	2
Unbiased assessment of the study endpoints	2	2	2	2	2	2
Follow-up period appropriate to the aim of the study	1	2	2	0	2	2
Loss to follow up less than 5%	2	0	2	0	0	0
Prospective calculation of the study size	0	0	0	0	0	0
Total	11	10	14	8	10	10

KEY: 1. Goshima et al, 2. Taylor et al, 3. Taylor et al 4. Abou-Zamzam et al,
5. Nicoloff et al, 6. Chung et al.

RESULTS

Description of studies

The literature search yielded 2,114 publications. A total of 1,147articles were selected after excluding irrelevant articles based on the titles and abstracts. With the application of our inclusion and exclusion criteria, 821 articles were selected over a 10-year period ending December, 2016. Based on human subjects above the age of 19 years, 590 articles were identified. Only six publications were identified as suitable for our study with three or more post-operative outcome measures (Fig 2). All six articles investigated three or more post-operative outcome measures (technical and/or functional). Technical outcome measures were based on the standards for reporting by the Society for Vascular Surgery/International Society for Cardiovascular Surgery (50), (51). The selected studies were of moderate quality using the MINORS scoring scale (Table 1). Five of them were retrospective studies and one was a prospective study (49). The six studies included a total of 2,446 patients (Table 2). The study population was grouped based on the investigated outcome measures and timelines at which the outcomes were assessed.

Fig 2: Flow Chart of Literature Search

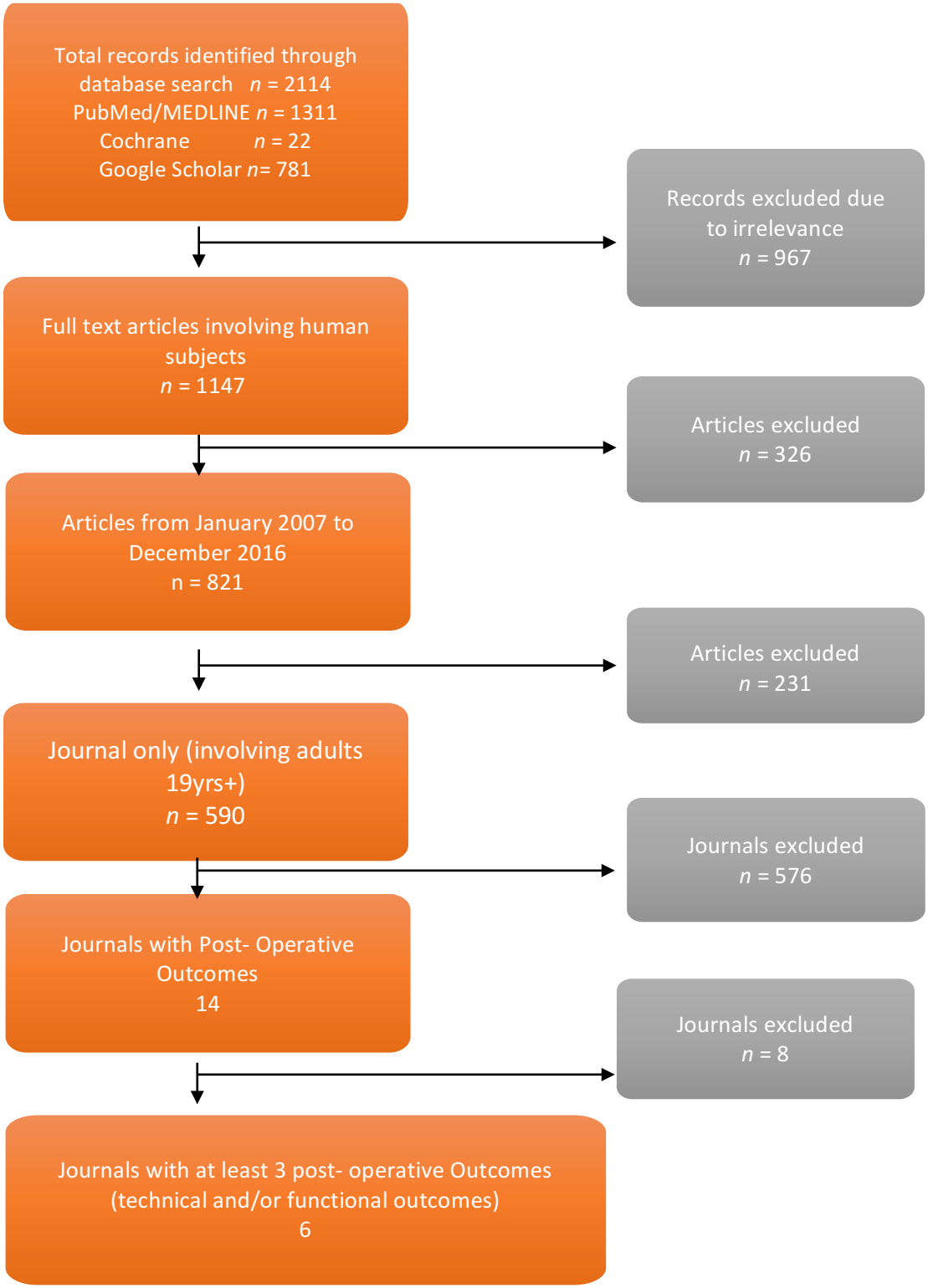


Table 2a: Included Studies

Study	n	Type of Study	Follow up (months)	Type of operation
Goshima et al 2004	315	Retrospective	Not reported	IBS
Taylor et al 2007	331	Retrospective	72	IBS SIB
Taylor et al 2006	841	Prospective	60	Open revascularization Endovascular intervention hybrid
Abou-Zamzam et al 1997	513	Retrospective	Not reported	IBS
Nicoloff et al 1998	112	Retrospective	36	IBS
Chung et al 2006	334	Retrospective	30	IBS
Total	2,446			

n = Number of Patients (Sample size)

Table 2b: Included Studies

Study		Goshima et al 2004	Taylor et al 2007	Taylor et al 2006	Abou-Zamzam et al 1997	Nicoloff et al 1998	Chung et al 2006
Limb Salvage (%)	6 months				94.2	94.9	85
	1 year		80.6	76.5			
	3 years					93.5	79.0
	5 years	91		72.1	85.2		
Primary Graft Patency (%)	6 months				92.0	93.1	
	1 year			76.6			63.0
	3 years					87.6	50.0
	5 years			72.4			
Ambulatory recovery (%)	6 months				80.0	92.0	72.0
	1 year		86.7				
	3 years					73.0	
	5 years			70.6			
Wound Healing (%)	6 months	54.0			12.0		42.0
	1 year						75.0

Outcome measures and predictive factors

Ambulatory recovery varied significantly, averaging 72% to 92% at six months; 86.7% at one year; 73% at three years and 70.6% at five years. Rates of local wound complications reported were between 12% and 24%. In some studies more than 50% of the ischaemic wounds took longer than three to four months to heal. In one study the wound healing rate at six months and one year was 42% and 75% respectively. Reported limb salvage rates were from 94.2% at six months to 76.5-85.0% at one year. The five years' limb salvage rates were 72.1-91%. Primary graft patency rate at one year was between 63% and 76.6%. On the whole 30-day mortality was <1% in most reports but one study reported 6.3%. Re-operation rates varied from 48.9% at three months to 50.5% at three years. Major amputation rates varied widely from 3.5% at three months to 23.2% at three years. Survival at six months, one year and five years were >80%, 89% and 48% respectively.

Multiple factors influence post-operative outcome. Tissue loss, high serum creatinine and diabetes (raised fasting plasma glucose) are associated with multiple re-operations and prolong wound healing (19), (45). Gangrene, diabetes, ESRD and impaired pre-operative ambulatory function predict low limb salvage, reduced graft patency and functional outcome (21), (46). Pre-operative impaired ambulatory

function was reported in most of the studies to be the most important predictor of sub-optimal post-operative functional outcome (21), (46), (47). A composite endpoint of limb salvage and ambulation at one year, survival at six months and graft patency up to the point of healing was achieved in only 44% of patients (20).

Some studies also investigated predictors of post-operative outcome but the spectrum of outcome measures assessed were fewer than the minimum of 3 selected for our study and therefore were excluded (52), (22). Other studies which investigated only one type of surgical intervention like PTA were excluded and studies with sample population of patients who had re-intervention for failed previous vascular interventions were also excluded (Table 3) (53), (54).

A total of six eligible studies reported seven outcomes of interest, however only five studies were used in conducting the meta-analysis. The study that was excluded from meta-analysis did not report the outcomes at the time lines of interest (*see Table 2*) (40-43, 68). Four studies were retrospective and one was prospective. Table 2 summarizes the included studies showing the number of patients, types of study, follow up, type of operation and outcomes. A total of 2,446 patients were included in this review.

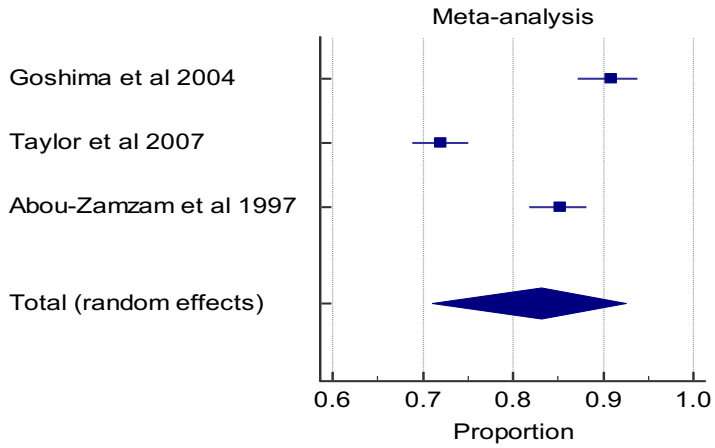
Table 3: Excluded Studies

Study	**Type of study**	***n***	**Reason for exclusion**	**Conclusion**
Kudo et al	Retrospective	192	Different objective (procedure volume over different time-period and outcomes)	open revascularization for the treatment of CLI have been largely replaced by angioplasty procedures without compromising outcomes
Vinit et al		331	Review	Patients with CLI should be offered revascularization if the procedure can be tolerated and the patient is ambulatory and living independently preoperatively. Amputation should be considered if the above criteria is not met.
Goodney et al	Retrospective	2,031	<3 post-operative outcome. Examined risk factors that predict amputation or graft	Risk factors can predict the risk of amputation and graft occlusion post-revascularization for CLI

			occlusion within the first year following lower extremity bypass.	
Simons et al	Retrospective	513	Less than 3 post-operative outcome measures investigated (assessed predictors of clinical failure defined as amputation and worsening ischaemia at 1 year)	10% of patients with patent grafts at 1year still could not attain clinical success. One of the predictors of failure to attain clinical success was ESRD.
Rutherford et al			Review	The initial published standards for reporting post-operative outcome for CLI requires periodic revision
Gibbons et al	Retrospective	318	Qualitative study	Baseline health status is a predictor of post-operative functional recovery and well-being.
Kudo et al	Retrospective	111	Evaluated post-operative outcome (effectiveness) of only percutaneous transluminal angioplasty (PTA)	PTA is feasible, safe and effective for the treatment of CLI
Ambler et al	Retrospective	90	Evaluated only 1 outcome measure, ambulation	Poor pre-operative ambulation predict poor post-operative ambulation and long LOS
Total		**3,586**		

n = Number of Patients (Sample size)

Figure 3a: Forest plot of meta-analysis of the proportion estimates for post-operative outcome: limb salvage

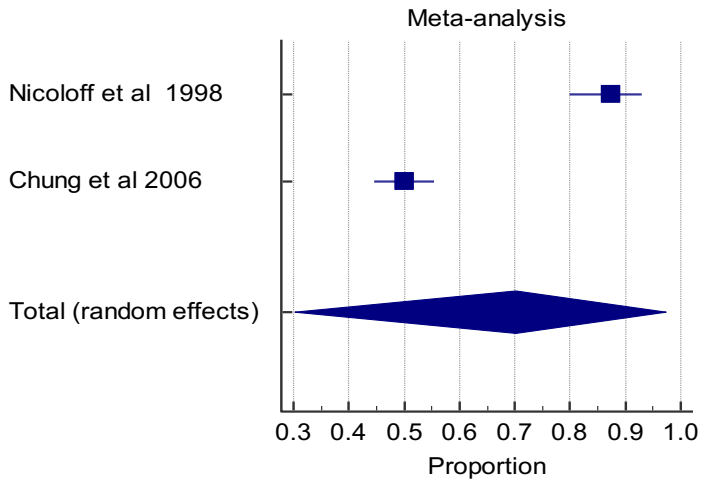


Study	Sample size	Proportion (%)	95% CI	Weight (%)	Test for heterogeneity	
				Random	Q	69.3607
Goshima et al 2004	318	90.881	87.166 to 93.807	32.82	DF	2
Taylor et al 2007	841	72.057	68.891 to 75.067	33.78	Significance level	P < 0.0001
Abou-Zamzam et al 1997	513	85.185	81.811 to 88.147	33.40	I^2 (inconsistency)	97.12%
Total (random effects)	1672	83.229	70.999 to 92.617	100.00	95% CI for I^2	94.24 to 98.56

Limb salvage

All 6 studies reported on limb salvage but at different time lines and follow up periods. At five years follow up, only three studies reported limb salvage outcome with Goshima et al reporting the highest percentage of 90.9% (40). The calculated pooled effect proportion using random-effects model among the three studies was 83.2%; (95% CI 71.0 to 92.6; n = 1672), with statistically significant heterogeneity (Cochran's Q test = Q = 69.4 on 2 degree of freedom, P <.0001, I^2 = 97%). Considerable heterogeneity existed between the three studies (Figure 3a).

Figure 3b: Forest plot of meta-analysis of the proportion estimates for post-operative outcome: primary graft patency

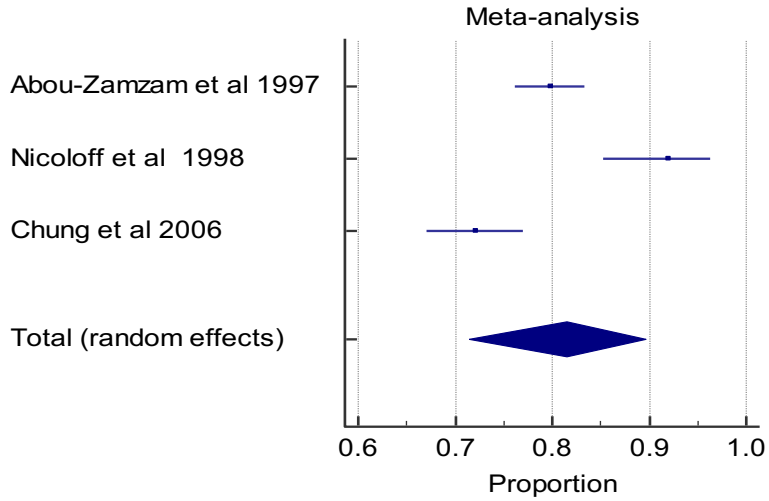


Study	Sample size	Proportion (%)	95% CI	Random	Test for heterogeneity	
					Q	59.3637
Nicoloff et al 1998	112	87.500	79.917 to 92.995	49.58	DF	1
Chung et al 2006	334	50.000	44.509 to 55.491	50.42	Significance level	P < 0.0001
Total (fixed effects)	446	60.492	55.797 to 65.048	100.00	I^2 (inconsistency)	98.32%
Total (random effects)	446	70.187	30.262 to 97.240	100.00	95% CI for I^2	96.22 to 99.25

Primary graft patency

Only four of the included studies reported on primary graft patency. At 3 years follow up, only two studies reported primary graft patency with Nicoloff et al. reporting the highest percentage of 87.5% (68). The calculated pooled effect proportion using random-effects model among the two studies was 70.2%; (95% CI 30.3 to 97.2; n = 446), with statistically significant heterogeneity (Cochran's Q test = Q = 59.4 on 1 degree of freedom, P <.0001, I^2 = 98%). Significant heterogeneity existed between the two studies (Figure 3b).

Figure 3c: Forest plot of meta-analysis of the proportion estimates for post-operative outcome: ambulatory recovery

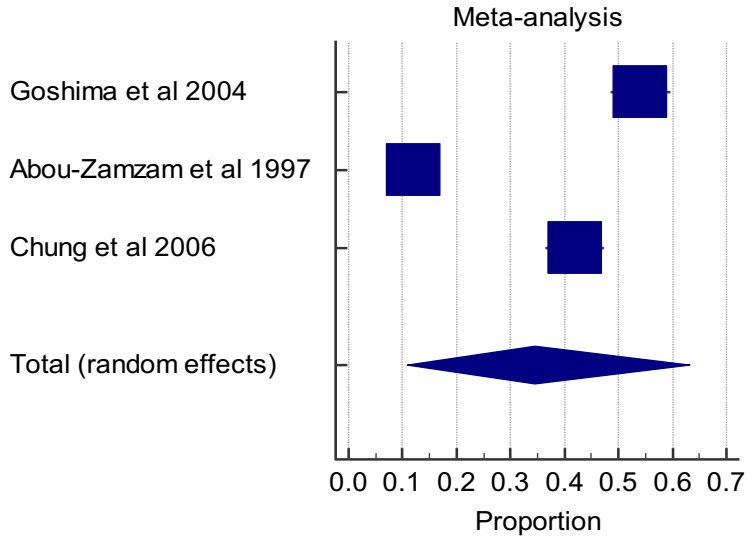


Study	Sample size	Proportion (%)	95% CI	Weight (%)	Test for heterogeneity	
				Random	Q	23.8936
Abou-Zamzam et al 1997	513	79.922	76.190 to 83.305	35.31	DF	2
Nicoloff et al 1998	112	91.964	85.293 to 96.260	30.25	Significance level	P < 0.0001
Chung et al 2006	334	72.156	67.016 to 76.897	34.44	I^2 (inconsistency)	91.63%
Total (random effects)	959	81.472	71.495 to 89.699	100.00	95% CI for I^2	78.61 to 96.73

Ambulatory recovery

Only three of the included studies reported on ambulatory recovery at six months follow up (41, 43, 68). Nicoloff et al reported the highest percentage of 92.0% (68). The calculated pooled effect proportion using random-effects model among the two studies was 81.5%; (95% CI 71.5 to 89.7; n = 959), with statistically significant heterogeneity (Cochran's Q test = Q = 23.89 on 2 degree of freedom, P = <.0001, I^2 = 92%). Figure 3c demonstrates considerable heterogeneity across the three studies.

Figure 3d: Forest plot of meta-analysis of the proportion estimates for post-operative outcome: wound healing



Study	Sample size	Proportion (%)	95% CI	Weight (%)	Test of heterogeneity	
				Random	Q	200.9922
Goshima et al 2004	318	54.088	48.437 to 59.662	33.28	DF	2
Abou-Zamzam et al 1997	513	12.086	9.393 to 15.224	33.43	Significance level	P < 0.0001
Chung et al 2006	334	41.916	36.567 to 47.410	33.30	I^2 (inconsistency)	99.00%
Total (random effects)	1165	34.571	10.951 to 63.280	100.00	95% CI for I^2	98.37 to 99.39

Wound healing

Wound healing among the patients was reported at six months of follow up by three studies. Goshima et al. (40) reported the highest percentage of wound healing among the study population at 54.0% while Abou-Zamzam et al. reported as low as 12.1% (43). The calculated pooled effect proportion using

random-effects model among the three studies was 34.6%; (95% CI 11.0 to 63.3; n = 1165), with statistically significant heterogeneity (Cochran's Q test = Q = 200.99 on 2 degree of freedom, P <.0001, I^2 = 99%). Considerable heterogeneity existed between the three studies (Figure 3d).

DISCUSSION

The literature search for the systematic review resulted in only six publications which met the eligibility criteria for our study. None of the publications studied patients' pre-operative metabolic profile in detail to assess any association with post-operative outcome. The total sample size of the six eligible studies was 2,446 (Sample size range: 112-841patients) with a mean follow-up 40.5 months for four studies. In the remaining two studies, the duration of follow up was not stated. Five of the six studies were conducted retrospectively. Patients' attrition rate was also poorly recorded except in one study. All six studies reported a combination of technical and functional outcomes. The combination of outcome variables varied among the studies and the timelines for outcome measures also varied widely. Of importance, five out of the six studies reported post-operative outcomes for only infrainguinal bypass; there was no inclusion of endovascular intervention or hybrid procedures. Goshima et al studied the outcomes after infrainguinal bypass surgery to determine risk factors for adverse outcomes. It was found that time to heal exceeded three months in >50% of patients and diabetes mellitus was a risk factor for prolong wound healing (19). In a study by Taylor et al, clinical success was defined as achieving all the following criteria: graft patency to the point of wound healing; limb salvage at one year; maintenance of ambulatory status for one year; and survival at six months. Despite > 70% limb salvage and graft patency at three years, only 44.4% of the patients achieved the composite endpoint of clinical success as stated above (20). Predictors of failure were the presence of gangrene, ESRD, hyperlipidaemia and impaired pre-operative ambulatory function. Taylor et al again examined the determinants of functional outcome after revascularization for critical limb ischemia. Findings were that, at five years, graft patency and limb salvage were acceptable at 70%. Functionally, however, at five years' survival was only 41% with 70% ambulatory recovery (21). The post-operative outcome was not influenced by the level of disease or type of operation. However, sub-optimal post-operative ambulation was predicted by poor pre-operative ambulatory function (21).

CONCLUSION

There is an enormous body of publication data on peripheral arterial disease. Most of the data however involve disease epidemiology, comparison of various treatment outcomes and experimental work on new treatment modalities. There is relatively little published data on metabolic profile and its impact on surgical treatment outcomes. This limits the effectiveness and quality of systematic review on that aspect of peripheral arterial disease research and accounts for the heterogeneity of the selected studies for the meta-analysis. That notwithstanding, using composite post-operative outcome measures for the evaluation of patients with CLI, many reports reveal that only a small proportion of patients with CLI who undergo surgical intervention attain full clinical success. This reinforces the fact that the traditional reporting standard of technical outcome is inadequate to fully evaluate patients' recovery post-operative. It is required that studies conform to uniform reporting standards with respect to timelines to overcome the significant heterogeneity among the studies depicted above. The summary result should therefore be interpreted with some level of caution. Multiple factors may influence post-operative outcomes including patients' metabolic profile. There is a desperate need to advocate for more prospective studies or even randomized trials with clearly delineated criteria for selection of participants and outcome assessment to improve upon the quality of existing studies and to facilitate comparison of results.

LIMITATIONS

1. Small number of studies elligible for the meta-analysis. This resulted in restricted analysis and non-comprehensive results.
2. Recall and selection bias due to the large number of retrospective studies

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Chapter 2

Metabolic profile and post-operative outcomes in contemporary patients with peripheral arterial disease and critical limb ischaemia: An observational prospective cohort study

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ABSTRACT

Metabolic profile and post-operative outcomes in contemporary patients with peripheral arterial disease and critical limb ischaemia- an observational prospective cohort study

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Background: Peripheral arterial disease (PAD) is an established occlusive disease of the peripheral arteries and is not uncommon in the elderly. Atherosclerosis accounts for 90% of the pathology. Only 15% of affected individuals become symptomatic. Most symptomatic individuals present with intermittent claudication (IC). Only a small proportion (1%) of affected individuals present with critical limb ischaemia (CLI). Revascularization aimed at limb salvage, and recovery of ambulation and independent living is the ultimate therapeutic option for the advanced form of PAD (CLI). Traditionally, the success of revascularization for CLI has been defined by graft patency rates and limb salvage rates. Functional outcomes such as ischaemic wound healing and recovery of ambulatory function for independent living have been the focus in more recent publications. However, these assessments do not consider the patients' pre-operative metabolic profile as a predictor of post-operative outcomes.

Purpose: The purpose of this study was to determine, in a prospective manner, the influence of pre-operative metabolic profile on post-operative outcomes in contemporary patients with peripheral arterial disease presenting with critical limb ischaemia at a tertiary hospital in South Africa.

Methods: All consecutive patients, ≥18 years, with CLI admitted to the vascular unit at Groote Schuur Hospital over a two-year period (1st January, 2015 to 31st December, 2016) with reconstructable disease were recruited for the study. Written informed consent was obtained from all participants. Revascularization entailed either open surgical revascularization, endovascular interventions or both (hybrid procedures). Data was analyzed according to the clinical level of disease and the type of surgical intervention. Post-operative outcome measures were determined.

Primary endpoints (functional and technical outcomes)

- Ambulatory recovery at six months and one year
- Complete ischaemic wound healing at six months and one year
- Limb salvage rate at six months and one year

- Primary graft patency rate at six months and one year

Secondary endpoint

- The influence of pre-operative metabolic profile on the post-operative outcomes

The association between pre-operative metabolic profile and post-operative outcomes was determined by Pearson Chi-square statistical test and logistic regression model.

Results: A total of 73 consecutive patients were recruited for this study with a mean age of 58 ± 9 years (Range: 30 - 75 years). Seventeen patients (23.3%) had rest pain and 56 (76.7%) had tissue loss [Minor tissue loss was 47 (64.4%) and major tissue loss was 9 (12.3%)]. Current smokers and previous smokers constituted 86% of the sample population with a male to female ratio of approximately 1:1. Our study population was generally overweight based on the BMI. There was high prevalence of abdominal obesity and high body fat for both males and females.
Recovery of ambulatory status was 69% and 67% at six months and one year follow-up respectively. The rate of ischaemic wound healing at six months and one year was 48.2% and 75.0% respectively. Surgical site sepsis was the most common local wound complication. Limb salvage rate was 78% and 79% at six months and one year respectively. Overall primary graft patency at six months was 69.0% but reduced to 60.0% at one year. Major amputation rate at one year was 21%. More than half of the patients who had major amputations presented to hospital late with major tissue loss (12.3% out of the 21%) requiring such major amputations. The rest had progressive disease after the initial presentation and treatment. Most of the post-operative wound-related complications occurred among patients with diabetes. More diabetic patients had major amputations compared to non-diabetic patients (57.9% vs 42.1%). One year amputation-free survival (AFS) was 69.9%. There were no statistically significant associations between metabolic profile of patients and post-operative clinical outcomes.

Conclusion: Demographics, co-morbidities, and procedural details of our study population, reflected a relatively younger population with CLI. The profile of this contemporary vascular surgery patients is that of overweight, high abdominal obesity, and high prevalence of smoking among both gender. The technical and functional outcomes observed in this study are consistent with available western literature. Diabetes was associated with prolonged ischaemic wound healing, higher risk of major amputation and local wound complications. A statistically significant association was not found between patients' metabolic profile and post-operative outcome but this could be due to the small sample size and short follow up period.

Keywords:
Peripheral arterial disease, critical limb ischaemia, revascularization, metabolic profile, post-operative outcomes

INTRODUCTION

Peripheral arterial disease (PAD) is a chronic occlusive disease of the peripheral arteries in the body with specific reference to the lower limbs. Atherosclerosis accounts for 90% of the pathology. This leads to narrowing (stenosis) or occlusion of the arteries and decreased lower limb perfusion. The result is exertional ischaemia classically in the calf muscles termed intermittent claudication (IC). In very severe disease, the reduced blood and oxygen supply is unable to meet even the resting metabolic rate. Therefore ischaemic foot pain develops in the recumbent position, typically at night, and is, unfortunately, termed rest pain. Critical limb ischaemia (CLI) is defined as rest pain of more than two weeks duration not responding to analgesics, the presence of tissue loss (ischaemic foot ulcer or gangrene), an ankle pressure of <50mmHg and toe pressure of < 30mmHg, (1) . In the presence of tissue loss in the ipsilateral lower extremity, the ankle pressure and toe pressures have been revised, by consensus (TASC II document), to >70 mmHg and >50 mmHg respectively (2).

The prevalence of PAD increases with increasing age (3). Therefore it is a problem worldwide due to increasing life expectancy globally. The prevalence is estimated at 12% among adults generally but up to 20% among those over the age of 70 years (4). The natural history of claudicants is essentially benign: approximately 75% of patients with IC either remain stable or actually experience symptom improvement due to metabolic, physiological and psychological adaptation. Critical limb ischaemia on the other hand is associated with a far worse prognosis (5). The annual mortality for individuals with IC is 5% but this increases sharply to about 20% in six months for those with CLI. This poorer prognosis of CLI relative to IC was noted in a study where 25% of patients with CLI progressed to major limb amputation within one year, and 25% died of cardiovascular complications within one year (6).

Clinically, affected individuals may be:

- Asymptomatic or
- Symptomatic (Intermittent claudication) or
- Complicated
    - Erectile dysfunction

- Acute limb ischaemia
- Critical limb ischaemia

Peripheral arterial disease is a clinical manifestation of systemic atherosclerosis. Therefore individuals with PAD also have increased risk of cardiovascular disease and cerebrovascular disease. Low ankle-brachial pressure index (ABI), a marker of the severity of PAD is also associated with increased cardiovascular mortality (7). Cardiac events alone accounts for a significant proportion of the mortality in patients with PAD (8), (9), (10). In addition to the high mortality experienced by people with CLI, there is also associated significant morbidity with respect to impaired ambulatory function and reduced quality of life (11),(12). The most significant morbidity associated with CLI is the high rate of limb loss (major amputations). In the case of patients with non-healing leg ulcer or gangrene, 25% of patients are cured, another 25% die from the disease, 30% end up with major amputation and 20% continue to experience symptoms of the disease one year following revascularisation (5).

Optimum medical therapy (OMT), lifestyle modification (exercise therapy, smoking cessation strategies; weight loss) and optimization of co-morbidities, particularly cardiovascular disease is the mainstay of treatment of patients with PAD irrespective of the clinical presentation (3). The use of pharmacological agents (statins; anti-platelet agents and certain anti-hypertensive medications) to reduce the progression of atherosclerosis, to reduce the risk of cardiovascular and cerebrovascular events, and improve survival and quality of life , is evidence-based and universally advocated. (13), (14), (14). Revascularization strategies, however, constitutes a significant component of the management of the advanced form of PAD (CLI). It is aimed primarily at limb salvage, but also to facilitate independent living.

Both medical and surgical treatment for PAD impose a huge financial burden either on the state or affected individuals due to the protracted course of the disease. The psychological stress for both patients and caregivers is enormous. One of the ways to reduce this huge burden of disease is to pre-operatively profile patients with PAD to determine any association with post-operative outcome with the aim of pre-operative patient optimisation to achieve improved post-operative outcomes.

A metabolic profile refers to an individual's physical/physiological wellbeing as assessed by anthropometric measurements and haematological and/or biochemical evaluation. It is a measure of one's immune competence to withstand adverse events such as trauma, major surgery and infections. It is also a measure of the body's capacity for wound healing. Surgical outcomes may be influenced by patients' factors such as pre-operative metabolic profile, extent of disease and co-morbidities. Other predictive factors of surgical outcome may be the mode of operation (open surgical reconstruction, endovascular intervention or both). In spite of the high burden of disease (3), there is limited research data globally, particularly in Sub-Saharan Africa on the effects of patients' pre-operative metabolic profile on post-operative outcome. This study objectively assessed the pre-operative metabolic profile of patients with CLI to determine any relationship with post-operative outcomes.

JUSTIFICATION OF THE STUDY

The prevalence of peripheral arterial disease varies widely with age (13), (14). Generally it ranges from 3% to10%, however for persons over 70 years it is between 15% and 20%,(3) . Thus, PAD prevalence clearly increases dramatically with age, (13), (14). It is also known to disproportionately affect the black population (13), hence the relevance of this study in South Africa. The REduction in Atherothrombosis for Continued Health Registry (REACH) has revealed that there is under-treatment of PAD relative to coronary artery disease (CAD) or cerebrovascular disease (CBVD), (14).

Majority of individuals with PAD have one or more cardiovascular disease risk factors with associated high morbidity and mortality. Pre-operative metabolic profile may play a significant role in the incidence of post-operative morbidity; particularly wound healing and major limb amputation rates. The aim of this study was to evaluate the influence of the pre-operative metabolic profiles of patients with CLI on post-operative morbidity and mortality. Findings from this study may influence patient selection to improve operative outcomes. It may also inform policy change regarding pre-operative patient optimization for surgery and thereby minimize post-operative morbidity and mortality.

AIM

To determine the influence of pre-operative metabolic profile on post-operative outcomes in contemporary vascular surgery patients with peripheral arterial disease presenting with critical limb ischaemia in a tertiary hospital in South Africa.

OBJECTIVES

1. To determine the demographic characteristics of patients with CLI
2. To determine the risk factors and metabolic profiles of participants
3. To determine the clinic-pathological characteristics of CLI
4. To assess technical and functional post-operative outcomes
5. To determine any association between metabolic profiles and post-operative outcomes

PATIENTS AND METHODS

Study design: An observational prospective cohort study, over a two-year period (1st January, 2015 to 31st December, 2016) was conducted to assess the influence of pre-operative metabolic profile on post-operative outcomes following revascularization for CLI in conventional risk patients. Consecutive eligible patients were recruited for this study. Follow up was for a period of one year. Data was collected manually using a datasheet and later processed digitally onto a Microsoft Excel spread sheet (2010 software). The data was subsequently abbreviated for statistical purposes and transferred to STATA version 14, for analysis.

The information collected was kept confidential. The soft copy was secured on a computer with password protection for access. The hard copy was kept secure in a locked cupboard in a protected office by the principal investigator. The data collected was not shared with or given to anyone else besides the researchers. Identity of participants was protected by the use of hospital numbers rather than actual patient names.

This study was approved by the Departmental (Surgical) Research Committee and the Human Research Ethics Committee of the University of Cape Town.

Setting: The study was carried out at the Vascular unit of Groote Schuur Hospital (GSH), Observatory, Cape Town. Groote Schuur Hospital is a tertiary hospital, the second largest hospital in South Africa, situated in the Western Cape.

Study population: All conventional risk adult patients (≥18 years old) with established PAD (critical limb ischaemia), and with reconstructable disease were recruited into the study. A written informed consent was obtained from all participants in this study.

Inclusion criteria:

- Established PAD
- CLI with rest pain
- CLI with ischaemic foot or leg ulcer
- CLI with gangrene of the foot (salvageable foot)
- Revascularization for stump salvage (Patients requiring major amputation in the clinical context of poor inflow or poor runoff)

Exclusion criteria:

- High risk surgical patients not fit for revascularization

- Patients with non-reconstructable disease on vascular imaging
- Patients who are unable to or who refuse to give informed consent
- Patients who are not independent
- Patients who are not ambulant (confined to a wheel-chair or bed-ridden)
- Patients who had previous revascularization

Information collected included basic demographic details, basic haematological and biochemical tests results, comorbidities, presence or absence of rest pain or tissue loss, length of hospital stay, and both pre-operative and post-operative ambulatory status. Data was collected by personal interviews and also from review of patients' hospital records. Patients pre-operative metabolic profiles were assessed using haematological and biochemical variables (haemoglobin, serum albumin, fasting plasma glucose, HbA1c). Anthropometric parameters (BMI, WHR, TSFT, MUAC) were measured using only one and the same non-stretch tape measure, weighing scale and calliper. Anthropometric measurements were assessed using the WHO definitions and instructions for measurement, appendix 6,7 and 8. Indication for surgical intervention was categorized into rest pain and ischemic tissue loss. Ankle-brachial pressure index (ABI) and arterial colour duplex (DUS) scanning were done for all patients before operation and at each follow-up out-patient clinic visit at one month, three months, six months and one year after the operation to check for graft patency. CT angiogram (CTA) or diagnostic peripheral angiogram (DSA) was done as and when indicated. Routinely, duplex ultrasound was done on both lower limbs but treatment was limited to the clinically symptomatic limb.
The type of surgical intervention (endovascular intervention, open surgical revascularization or hybrid procedure) was noted. Any additional operation and re-operations after the index revascularization procedure (minor/major amputation, wound debridement) were recorded. Local wound complications, time to wound healing, ambulatory recovery, level of amputation, limb salvage and primary graft patency were determined.

Definitions:

- Wound healing assessment was by prevalence of local wound complications and by the proportion of ischaemic and surgical wounds which healed completely by six months and one year.
- Ambulatory status was irrespective of whether it was indoors or outdoors
- Major amputation referred to any amputation above the level of the ankle (BKA, TKA, AKA, hip disarticulation).

- Minor amputation referred to any foot amputation not requiring a prosthesis to mobilize
- Limb salvage is defined as the absence of major amputation following revascularization
- Primary graft patency was determined at each OPD visit with DUS. Grafts were considered patent if the PSV was < 180cm/s, velocity ratio <2, flow in the graft >45cm/s and ABI drop following exertion not > 15%
- Re-operation referred to repeat ischaemic foot ulcer debridement, debridement for surgical site sepsis and minor foot amputation as a staged procedure following revascularization.
- Re-intervention referred to any repeat ipsilateral open surgical or endovascular procedure following revascularization for CLI.

Regular post-operative scheduled clinic visits (one month, every three months for the first year, and every six months for the second year), was observed. Patients with complications were seen more frequently or re-admitted for further treatment when indicated. Additionally, patient follow-up was augmented with telephone calls directly to the patients or patients' relatives in the case of deceased patients.

Statistical consideration:

Sample size: On average, 2 revascularization procedures (endovascular, open revascularization or hybrid procedure) are done per week, i.e. 8 cases in a month. Expected number of revascularization procedures in 2 years is 192.

A sample size of 96 achieves 85% power to detect a difference of 0.30000 between the null hypothesis correlation of 0.00000 and the alternative hypothesis correlation of -0.30000 using a two-sided hypothesis test with a significance level of 0.05000.

Ho: There is no association between post-operative outcomes (dependent) variables and metabolic profile (independent variables).

Ha: There is an association between post-operative outcomes (dependent) variables and metabolic profile (independent variables).

Where *Ho* = Null hypothesis

Ha = Alternative hypothesis

The significance level to reject the null hypothesis is set at 0.05 ($\alpha = 0.05$)

Data management and analysis:

Descriptive statistical analysis was conducted to describe the demographic and clinico-pathological characteristics of the study population. Continuous variables were presented as mean, standard deviation, box and whisker plot for normal distribution data. Categorical variables were presented as proportions, bar charts and pie charts. Median, interquartile range (IQR) and line graphs were used for skewed data.

Functional and technical post-operative outcome measures were presented using actuarial life-table method (Kaplan-Meier analysis). Pearson Chi-square statistical test was conducted to determine the association between the independent and dependent variables. Logistic regression model was conducted to adjust for multiple confounders. Odd ratio, 95% confidence interval and P value <0.05 were used to test the hypothesis.

RESULTS

Patients' profile

The mean follow-up in our study was 9.9 months (Range: 3-22months), 73 patients were available for analysis, four patients were lost to follow up. The overall mean age of the study population was 58 ± 9 years (Range: 30-75years). There were 36 (49.3%) females and 37 (50.7%) males(Table 1). The mean age at presentation was 60.9 years for females (Range: 34-75years) and 55.1 years for males (Range: 30-70years), (p value < 0.01), (Fig 1). Table 2 shows the risk factor prevalence and co-morbidities of patients. Smoking was the most predominant risk factor in the study population with a prevalence of 86.3% (current smokers and ex-smokers) and a male to female ratio of 1:1. Only 13.7% of the patients had never smoked. Table 3 shows the pattern of anti-diabetic and anti-hypertensive treatment. Less than 50% of the patients were on statins at admission in this study. In contrast, the proportion of patients on aspirin at the time of admission was relatively high at 74.0%.

Table 1: Clinical level of disease and gender distribution

	No. of patients	**Gender**	
Clinical level of disease	***n* (%)**	**Male *n***	**Female *n***
Aorto-iliac disease	16 (21.9%)	10	6
Fem-pop disease	48 (65.8%)	21	27
Tibio-peroneal disease	9 (12.3%)	6	3
Total	73 (100%)	37	36

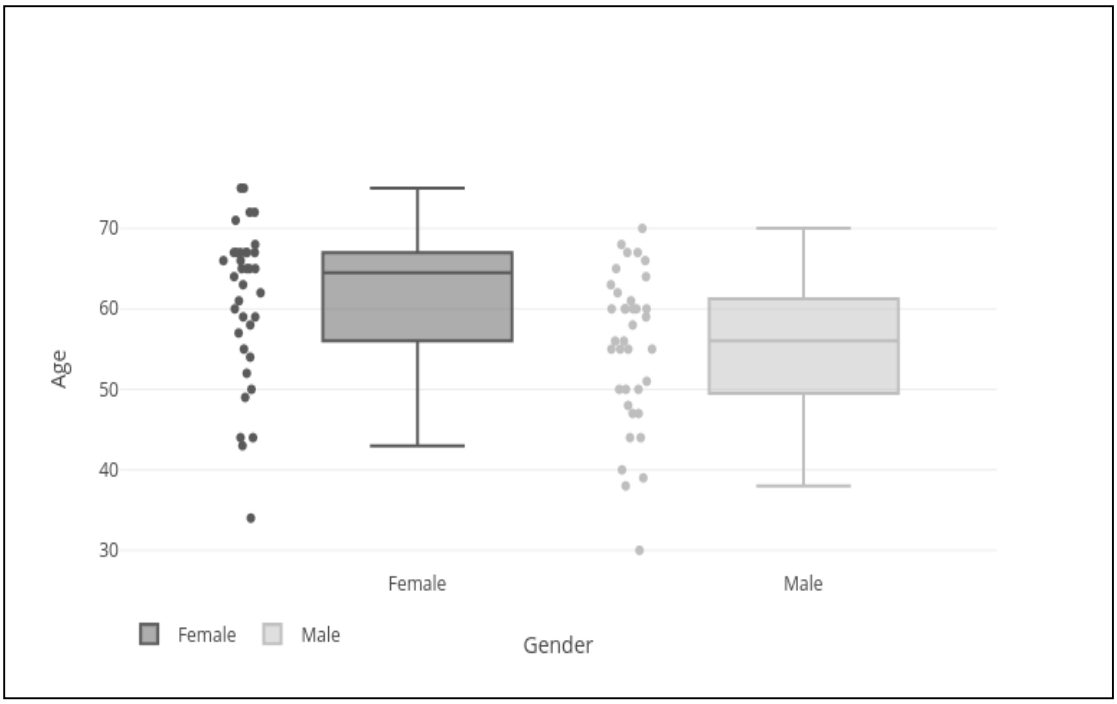

Fig. 1 Age and gender distribution

Table 2: Prevalence of risk factors and comorbidities

	Clinical level of disease			
	Aorto-iliac ***n*** **(%)**	**Fem-pop** ***n*** **(%)**	**Tibio-peroneal** ***n*** **(%)**	**Total** ***n*** **(%)**
Total Number of patients (*n* =73)	16(21.9%)	48(65.8%)	9(12.3%)	73(100%)
Smokers	12(75.0%)	23(48.0%)	4(44.4%)	39(53.4%)
Ex-smokers	2(12.5%)	20(41.7%)	2(22.2%)	24(32.9%)
Diabetes	4 (25.0%)	35 (72.9%)	5(55.6%)	44 (59.5%)
Hypertension	11(68.8%)	40(83.3%)	8(88.9%)	59(80.8%)
Hypercholesterolemia	7 (43.8%)	25 (52.1%)	6(66.7%)	38 (52.1%)
Cerebrovascular disease				11(15.1%)
Coronary artery disease				5(6.8%)
Chronic kidney disease				2(2.7%)

Table 3: Pattern of anti-diabetic and anti-hypertensive medication

Diabetic patients	***n***	**%**
Oral hypoglycemic agent	27	61.36
Insulin	6	13.64
Both	11	25
Total	44	100
Hypertensive patients	***n***	**%**
Single Agent	15	25.42
2 or more agents	44	74.58
Total	59	100

Disease profile

Seventeen patients (23.3%) had rest pain and 56 (76.7%) had tissue loss [Minor tissue loss 47 (64.4%) and major tissue loss 9 (12.3%)], (Table 4). The average duration of symptoms was 13.7 ± 13 weeks (Range: 0.7 - 68.5 weeks) (Fig 2). Table 5 shows the TASC grading of disease profile. The mean ankle pressures and ABIs are shown in Table 6. Duplex ultrasound was the initial imaging modality in all patients (Fig 3). The patency of crural vessels assessed by imaging investigation revealed that 31.5% of the patients had only one crural vessel patent, 32.9% had two patent vessels, 24.7% had all three vessels patent and 10.9% had no patent crural arteries, fig 4.

Table 4: Clinical level of disease: Rutherford clinical category

	Rutherford category		
Clinical level of disease	**4 (rest pain)**	**5 (minor tissue loss)**	**6 (major tissue loss requiring a major amputation)**
Aorto-iliac disease	6 (37.5%)	10 (62.5%)	0 (0%)
Fem-pop disease	11 (22.9%)	29 (60.4%)	8 (16.7%)
Tibio-peroneal disease	0 (0%)	8 (88.9%)	1 (11.1%)
Total	17(23.3%)	47(64.4%)	9(12.3%)

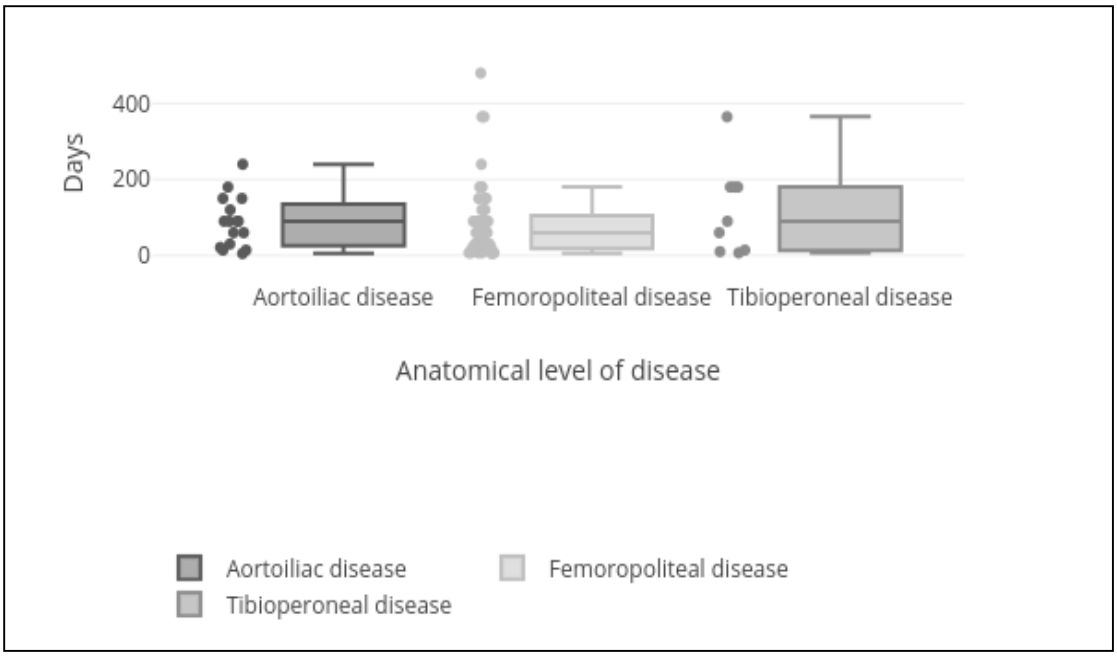

Fig. 2 Duration of symptoms of disease

Table 5: Clinical levels of disease: TASC grading

	TASC grade			
Clinical level of disease	**A**	**B**	**C**	**D**
Aorto-iliac disease	0 (0%)	1 (6.2%)	7 (43.8%)	8 (50%)
Fem-pop disease	3 (5.3%)	16 (33.3%)	25 (52.1%)	4 (8.3%)
Tibio-peroneal disease	1 (11.1%)	1 (11.1%)	6 (66.7%)	1 (11.1%)
Total	4(5.4%)	18(24.7%)	38(52.1%)	13(17.8%)

Table 6: Clinical level of disease: Ankle pressures and ankle brachial pressure index (ABI)

	Ankle pressures				
Clinical level of disease	***n***	**$\bar{x}$**	**SD**	**Min**	**Max**
Aorto-iliac disease	16.0	26.6	33.5	0.0	100.0
Fem-pop	48.0	71.1	67.1	0.0	260.0
Tibio-peroneal	9.0	131.7	61.5	60.0	260.0
	Ankle brachial pressure index (ABI)				
Aorto-iliac disease	16.0	0.18	0.22	0.00	0.50
Fem-pop	48.0	0.47	0.40	0.00	1.50
Tibio-peroneal	9.0	0.68	0.36	0.38	1.50

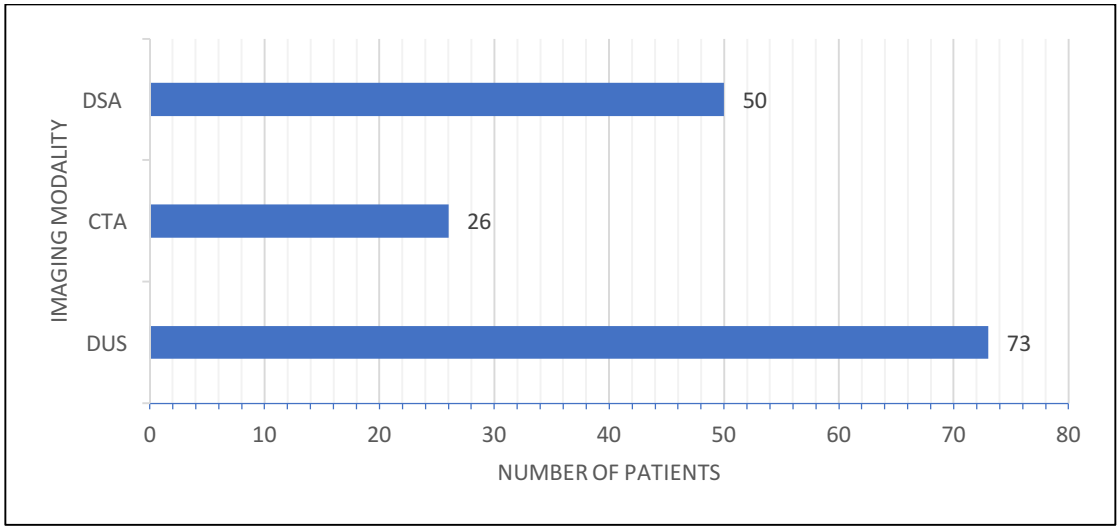

Fig. 3 Pre-operative imaging modalities

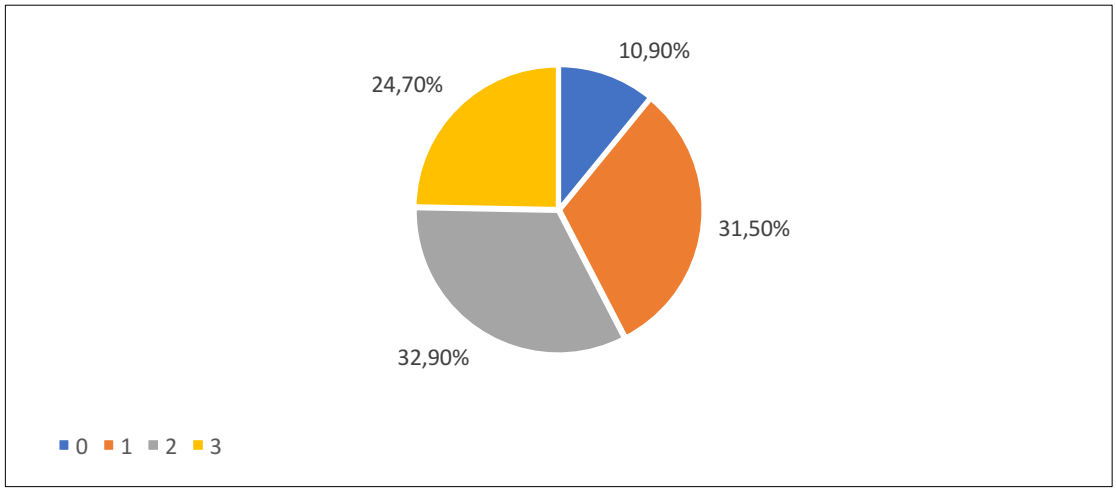

Fig. 4 Number of patent crural arteries

Metabolic profile

The anthropometric, haematological/biochemical measurement are shown in tables 7 and 8. The overall mean body mass index (BMI) was 26.04. Twenty four (32.8%) patients had BMI >25.0 and thirteen (17.8%) patients had BMI >30.0. The mean waist: hip ratio (WHR) was 0.96, (0.99 for males and 0.93 for females). The overall mean haemoglobin level was 12.5g/dl (SD 2.5, min. 6.1, max. 18.5). The mean for males and females were 13.2 g/dL and 14.2 g/dL respectively. There were two patients with confirmed diagnosis of chronic renal disease but only one patient had a creatinine of >120 µmol/L on admission. The mean serum albumin was 3.8 g/L (SD 5.8, min. 2.8, max. 5.1). Forty-four patients were known with diabetes. Two (6.9%) out of the 29 patients who were not previously diagnosed with diabetes had a HbA1c > 10% (newly diagnosed diabetes on admission). Average fasting plasma glucose in diabetic patients was 8.9 µmol/L . The average HbA1c in diabetic patients was 8.8 µmol/L.

Table 7: Anthropometric measurements

	n	$\bar{x}$	SD	min	max
Parameters	**Males**				
BMI- (kg/m^2)	37	24.98	4.27	16.85	34.52
WHR	35	0.99	0.07	0.86	1.16
TSFT-(mm)	33	12.57	4.01	6.00	20.30
MUAC-(cm)	35	28.49	3.62	20.00	36.00
	Females				
BMI- (kg/m^2)	35	27.16	7.26	17.31	45.96
WHR	35	0.93	0.16	0.09	1.12
TSF-mm	36	12.75	4.80	3.90	25.00
MUAC-(cm)	35	28.46	5.02	21.00	43.00
	Whole group				
BMI - (kg/m^2)	72	26.04	5.97	16.85	45.96
WHR	70	0.96	0.13	0.09	1.16
TSFT-(mm)	69	12.66	4.41	3.90	25.00
MUAC-(cm)	70	28.47	4.34	20.00	43.00

BMI	Body mass index
WHR	Waist-hip circumference ratio
TSFT	Triceps skin fold thickness
MUAC	Mid-upper arm circumference

Table 8: Haematological and biochemical parameters

Parameters	n	$\bar{x}$	SD	min	Max
Haemoglobin (g/dl)	73	12.5	2.5	6.1	18.5
White cell count($x10^9$/L)	73	11.2	3.5	6.1	24.7
Platelet count ($x10^9$/L)	73	389.9	150.1	156.0	963.0
INR	73	1.08	0.14	0.85	1.9
Serum creatinine (µmol/L)	67	72.9	23.0	32.0	187.0
Serum albumin(g/L)	67	3.8	5.8	2.8	5.1
Fasting plasma glucose (group)(mmol/L)	68	7.8	3.0	3.0	15.6
Fasting plasma glucose (DM only) (mmol/L)	41	8.9	3.2	3.0	15.6
HbA1c (DM only)	41	8.8	2.3	4.3	13.5
HbA1c (non-DM only)	23	6.0	1.4	5.0	10.8

Treatment outcomes

A third of the study population (31.5%) had endovascular interventions, 58.9% had open revascularization (autologous vein 41.9% and prosthetic grafts 58.1%) and 9.6% had hybrid procedures, (Fig 5). Surgical site sepsis was the most common surgical wound complication (Table 9). There were two (4.7%) cases of early graft sepsis, (both were PTFE grafts) and two (4.0%) cases of early graft occlusion (PTFE graft). Fifty-six patients had ischaemic wounds and 36 of them were known with diabetes mellitus (Fig. 13). Only 48.2% of the ischaemic wounds healed by six months. At one year follow up 75% of the ischaemic wounds had healed (Fig 13). Thirteen diabetic patients and five non-diabetic patients had septic ischaemic wounds at admission. Out of the 12 cases of surgical site sepsis, 10 occurred in diabetic patients compared to two in non-diabetic patients(Table 9).

Mean length of hospital stay was 17.5 days (SD: 17.7, Range: 3 days to 110 days). Table 10 a and Table 10b show some of the results of test of association of the patients' metabolic profile and post-operative outcomes. The presence of co-morbidities such as cerebrovascular disease, coronary artery disease and chronic kidney disease was not found to be associated with post-operative outcome. This may be due to the small number of patients with such co-morbidities in our study.

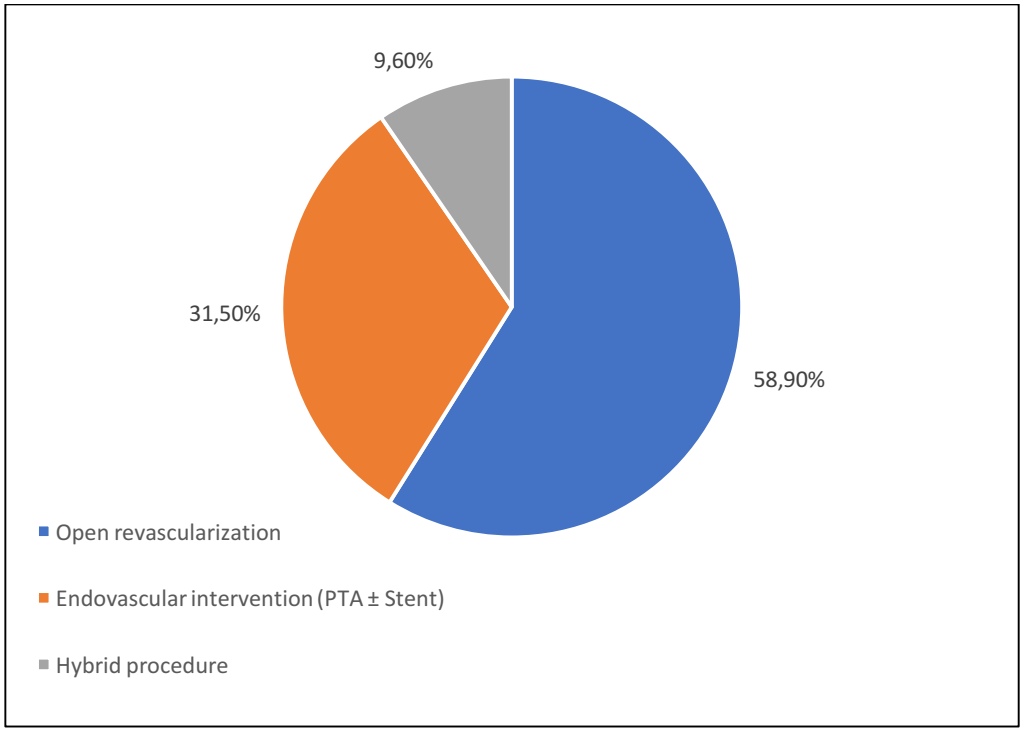

Fig. 5 Type of surgical intervention

Table 9: Early post-operative complications

	Type of surgical intervention		
	Open revascularization n (%)	**Endovascular intervention n(%)**	**Hybrid procedure n(%)**
Surgical site sepsis	9 (20.9%)	0 (0%)	3 (42.9%)
Seroma/Haematoma	2 (4.7%)	1 (4.3%)	0 (0%)
False aneurysm	1 (2.3%)	0 (0%)	0 (0%)
Graft sepsis	2 (4.7%)	0 (0%)	0 (0%)
Graft occlusion	1 (2.3%)	0 (0%)	1 (14.3%)
Total	15 (34.9%)	1 (4.3%)	4 (57.2%)

Number of patients who had open revascularization = 43

Number of patients who had endovascular intervention = 23

Number of patients who had hybrid procedure = 7

Table 10a: Test of association between metabolic profiles and post-operative outcomes at 6 months

Dependent variables (Metabolic profile parameters combined with post-operative outcome. Bivariate or univariate analysis)	Univariate analysis		
	Odd's ratio	95% confidence interval	p-value
BMI< 25	0.66	0.16 to 2.46	0.49
WHR <0.9	0.27	0.05 to 1.50	0.06
TSFT <11	1.70	0.44 to 7.28	0.39
MUAC<26	3.2	0.58 to 32.74	0.14
Hb<10g/dl	2.11	0.36 to 22.18	0.37
Fasting plasma glucose <6.1	1.11	0.27 to 4.27	0.86
HbA1c <7	1.20	0.32 to 4.65	0.76
Albumin<3,5	0.94	0.23 to 4.24	0.93

Table 10b: Test of association between metabolic profiles and post-operative outcomes at 6 months

Dependent variables (Metabolic profile parameters combined with post-operative outcome. Bivariate or univariate analysis)	Univariate analysis		
	Odd's ratio	95% confidence interval	p-value
BMI>25	0.46	0.10 to 1.76	0.21
WHR >0.9	0.46	0.09 to 2.76	0.29
TSFT >16.5	1.29	0.19 to 14.39	0.77
MUAC>29	0.59	0.16 to 2.17	0.37
Hb>10g/dl	2.11	0.36 to 22.18	0.37
Fasting plasma glucose >6.1	1.11	0.27 to 4.27	0.86
HbA1c >7	0.59	0.15 to 2.23	0.38
Albumin>3.5	0.63	0.16 to 2.67	0.46

DISCUSSION

Our study population was predominantly middle-aged with a male to female ratio of 1:1. Females presented at a significantly older age than men (p value < 0.01). More than half (50.6%) of our study population was either overweight or obese. Smoking was the predominant risk factor for atherosclerosis with equal prevalence among males and females. The high number of females affected may be explained by the high prevalence of smoking among females (77.8%). Patients generally presented to hospital after ten weeks from the start of symptoms usually with a more advanced clinical presentation. The age of patients in our study population is lower than that in existing Western literature, (2), (11), (15), (16), (17). The male to female ratio in our study also differs significantly from the 3:1 ratio reported in existing Western literature (15), but similar to findings in a study in Uganda, (18). Similar to other reports, there were more patients with tissue loss in our study than rest pain only, (19), (20), (21). The pattern and distribution of occlusive disease is consistent with the study by Taylor et al, with more infra-inguinal disease than aorto-iliac disease (22). The small number of patients with TP disease may be due to selection bias for intervention. Most of our patients with isolated TP disease have poor runoff and very calcified vessels precluding them from revascularization. It is acknowledged however, that there are some publications that show good post-operative outcomes following revascularization for patients with isolated TP disease and tissue loss, (3). The overall mean duration of symptoms of 13 weeks is longer than was found by Bailey et al. in a one-year prospective study, (23). The much longer duration of symptoms for TP disease compared to the other clinical levels of disease may be explained by the least amount of ischaemic tissue due to the distal location of the occlusive disease (Fig 2). More than 50% (five out of a total of nine) of the patients with TP disease were confirmed to have diabetes mellitus. Diabetic peripheral neuropathy, poor socio-economic circumstances and travel issues may also account for the delay in clinical presentation in this group.

The pattern of pre-operative ankle pressures and ABI for the various clinical levels of disease, shown in Figures 6 and 7, is consistent with the existing literature. The high ankle pressures and ABI among the patients with TP disease could be due to the high prevalence of diabetes (55.6%) among such patients with associated calcified non-compressible crural arteries (medial calcinosis).

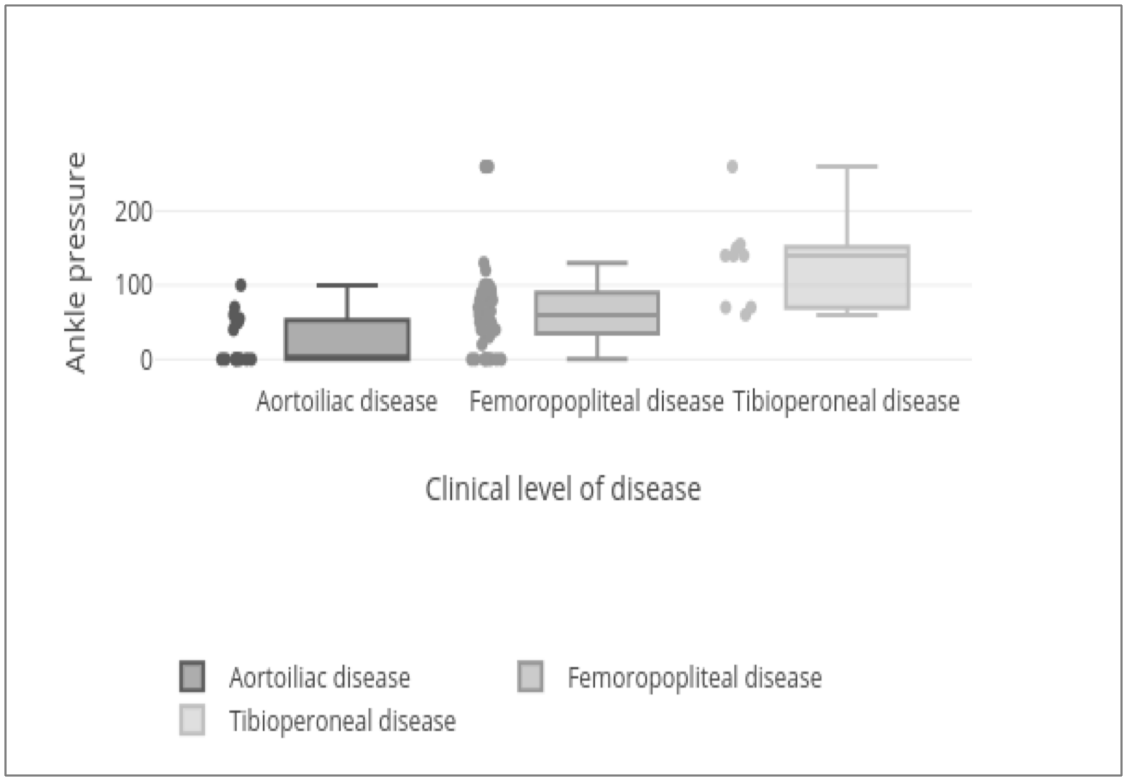

Fig. 6 Pre-operative ankle pressure by clinical level of disease

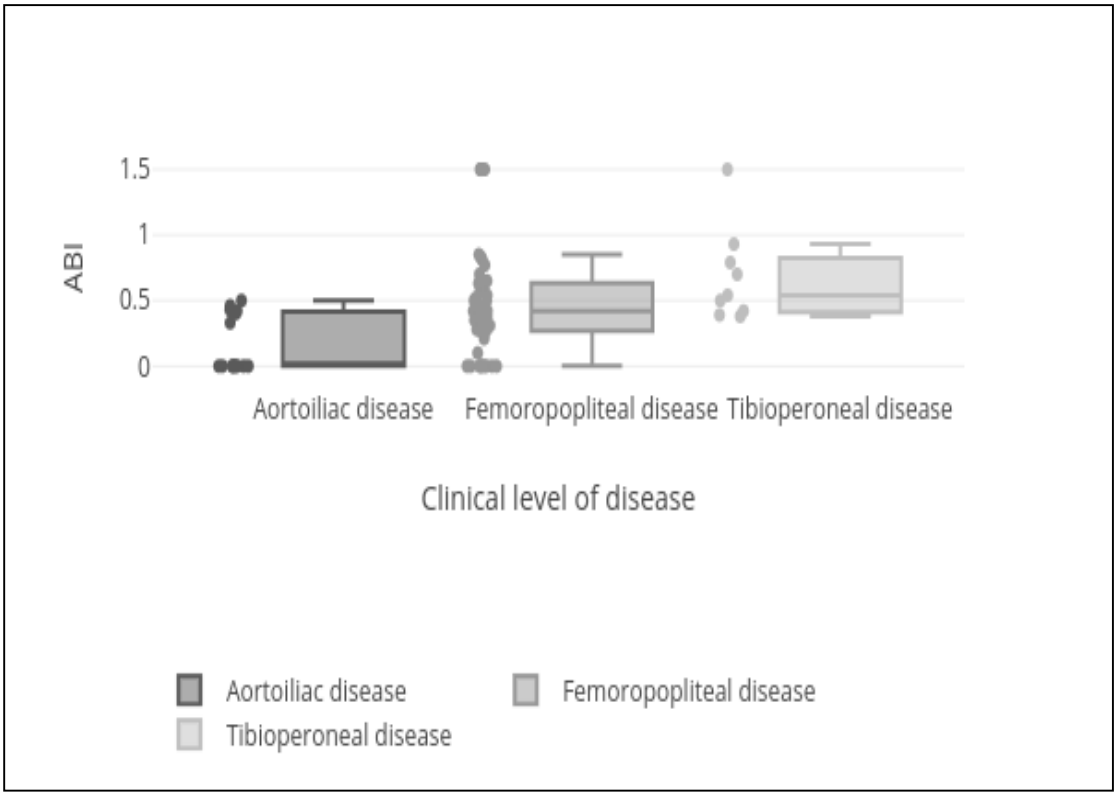

Fig. 7 Pre-operative ABI by clinical level of disease

Patients who had endovascular intervention had higher pre-operative ABIs than those who had open reconstruction or hybrid procedure, (Fig.8). This is suggestive of less severe disease among patients who had endovascular intervention and is in agreement with the TASC recommendation. The post-operative increase in ABI followed a similar trend, (Fig 9). The increase in ABI in the immediate post-operative period was sustained up to one year, (Fig 10). Eleven percent of the patients had no patent runoff vessels but had revascularization as an inflow procedure for stump salvage (Fig 4).

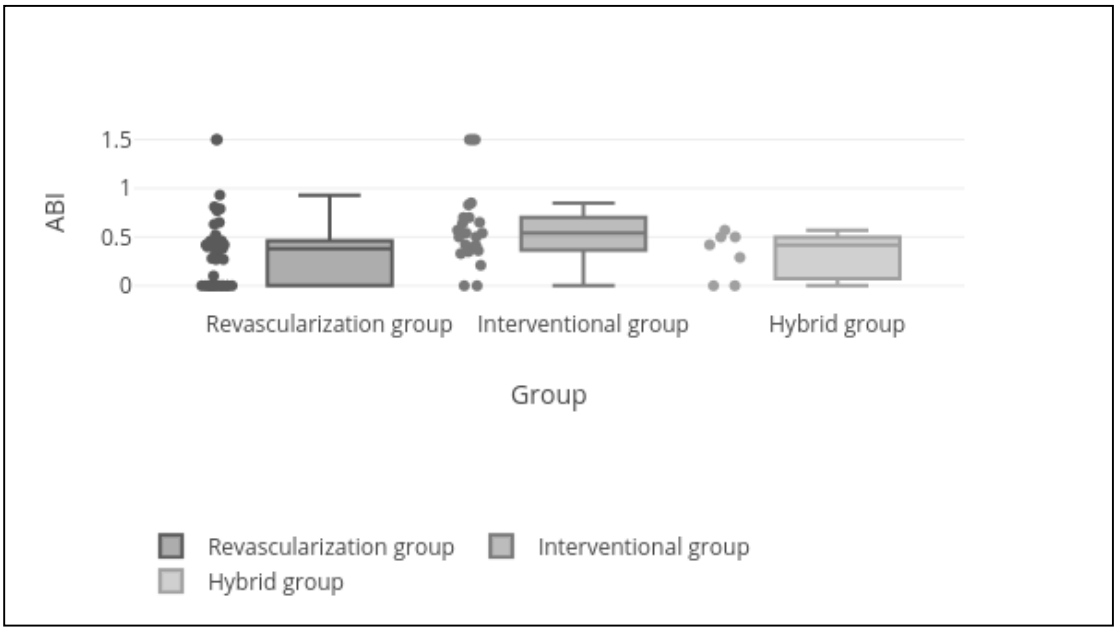

Fig. 8 Pre-operative ABI by the type of operation

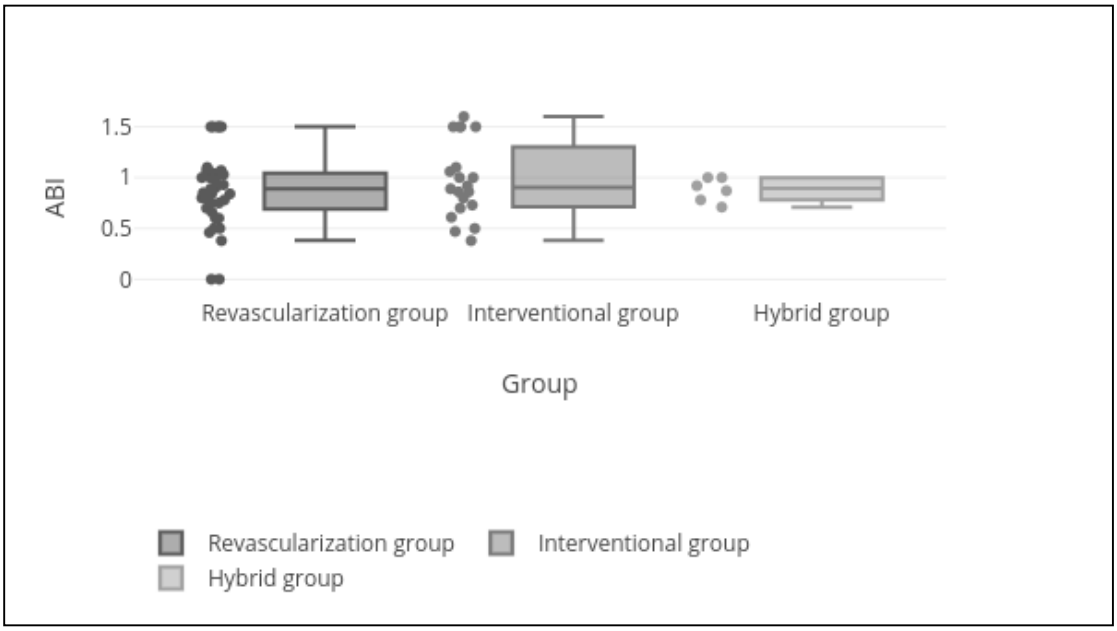

Fig. 9 Post-operative ABI by the type of operation

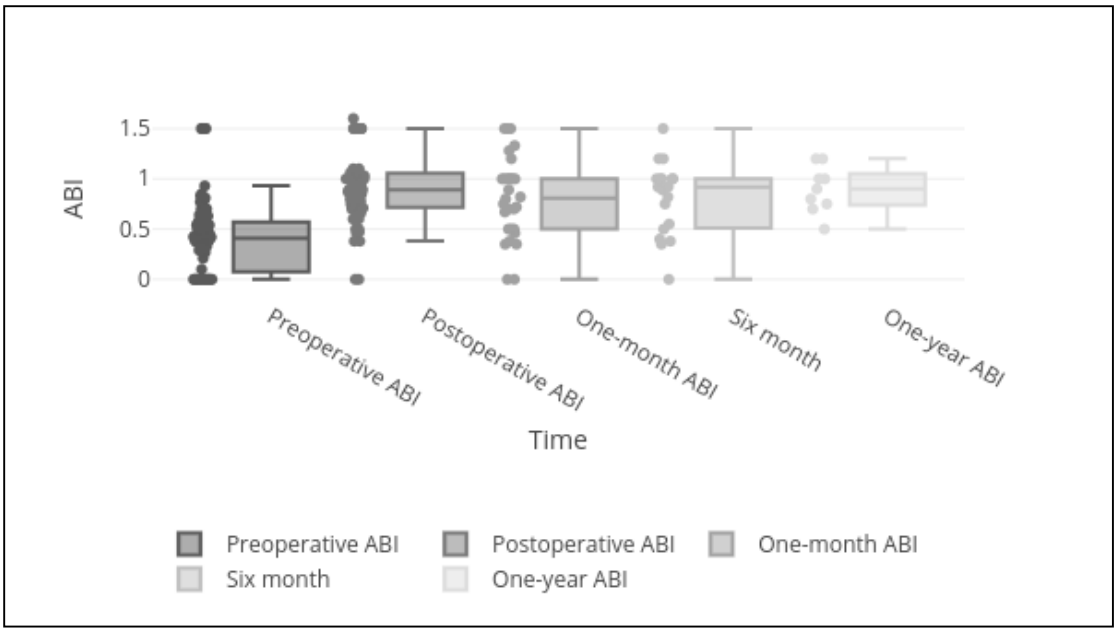

Fig. 10 ABI trend from pre-operative to post-operative period

The prevalence of risk factors for atherosclerosis, in our study population, is consistent with existing Western literature with smoking being the most prevalent risk factor (86.3%) (Table 2), (3), (22), (23). All our hypertensive patients were on some form of anti-hypertensive treatment. A significant number of them (74.58%), however, were on 2 or more agents. Ten (16.9%) patients had poorly controlled BP (Normal BP defined as <140/90mmHg). The low level of statin medication (47.97%) in our study population at baseline is consistent with findings in other studies like the PREVENT III study where only 46% of the participants were on lipid lowering medication (24), (25), (26). In contrast however, a larger proportion of our patients were on antiplatelet therapy (aspirin) compared to that in the PREVENT III study (74.0% vs 67%). This may be due to the high percentage of patients with hypertension among our study population. Most of such patients were started on aspirin (74%) in addition to anti-hypertensive medications (80.8%) by the general practitioner prior to referral to the vascular surgeon, (Table 3) (24). The prevalence of cardiovascular co-morbidities, particularly symptomatic CAD, is relatively low among our study population compared with other reports, (Table 2), (18), (24), (27). This may be due to the relatively younger age of our study population.

Metabolic profile

BMI is a measure of body size and composition. It is used to diagnose underweight, overweight or obesity. However, alternative measures that reflect abdominal adiposity like WHR, have been suggested as being superior to BMI in predicting CVD risk. Increased visceral fat is associated with metabolic abnormalities viz. impaired glucose tolerance, reduced insulin sensitivity and adverse lipid profiles. These are risk factors for type 2 diabetes and CVD. Overall, our study population was overweight with

a mean BMI of 26.0, (Table 7), (3), appendix 6. Both males and females in our study have abdominal obesity according to the WHO definition, (Table 7; Appendix 7).

Table 8 shows that the patients with diabetes have poor glycaemic control (Optimal glycaemic control defined as HbA1c of ≤7%), similar to findings in a study in Uganda,(23).

Outcome measures

In our study, open surgical revascularization was the predominant surgical intervention similar to the study by Bailey et al. and Taylor et al. but at variance with recent studies where endovascular intervention is the most frequent surgical treatment (24), (25).

Traditionally, the reporting standards for success of lower limb revascularization for CLI is as published by Rutherford et al. (28), (29). This is hinged on technical outcome measures of limb salvage, graft patency and survival. Subsequently, many recent publications including that by Taylor et al suggested that functional outcome measures, such as wound healing, recovery of ambulatory status, and amputation free survival are better outcome measures for assessing clinical success,(30), (23), (27), (24), (31). Using composite endpoints (technical and functional outcome measures) for the evaluation of post-operative outcomes revealed that only a small proportion of patients with CLI who undergo surgical intervention attain full clinical success (29).

In our study, post–operative outcome was assessed by both technical (surgeon-oriented) measures such as limb salvage and primary graft patency and functional (patient-oriented) measures such as local wound complication rate, ambulatory recovery, mortality rate and minor/major amputation rates. At one year follow up in our study, ambulatory recovery was 67%, primary graft patency was 60% and limb salvage was 79%, (Fig. 11). One year primary graft patency rate of 60% to 80% and limb salvage rates of 70% to 90% have consistently been reported after treatment of CLI and is consistent with findings in our study (32). Pre-operative ambulatory status predicted post-operative ambulatory recovery, similar to the findings in other studies (33), (34).

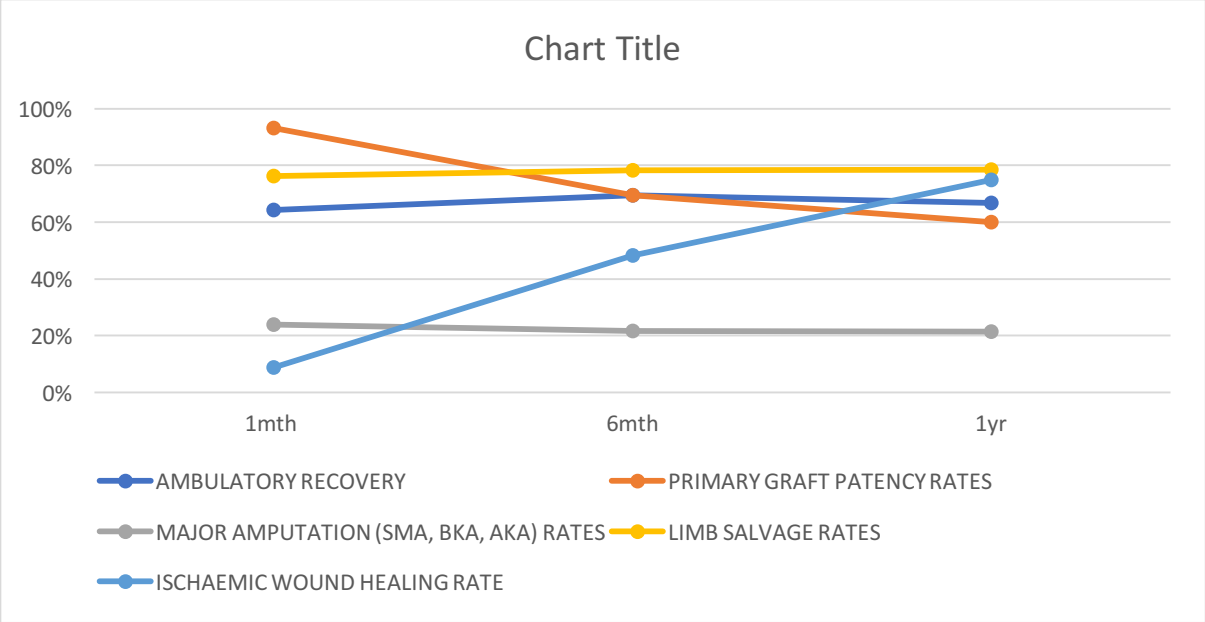

Fig. 11 Trend of post-operative outcomes

The overall one year major amputation rate of 21% in our study is similar to the 23.2% found in the study by Nicoloff et al. and in TASC II, (22), (35). In this study we included conventional risk patients with PAD and CLI requiring revascularization for stump salvage (Requiring a major amputation anyway). Less than 50% of ischaemic wounds healed at six months in our study population. Diabetic patients experienced more ischaemic wound sepsis and surgical site sepsis than non-diabetic patients (29.5% vs 17.2%) and (83.3% vs 16.7%) respectively. Overall early graft sepsis rate was 4.7% and early graft occlusion rate was 4.0%. The graft occlusion rate is comparable to findings by Goshima et al, with a 30 day graft occlusion rate of 3.1%, (36). More diabetic patients in our study had major amputations than non-diabetic patients (57.9% vs 42.1%), (34), (37). The overall surgical site sepsis rate was 24.0% and occurred among patients treated with open revascularization and hybrid procedure but none among the endovascular intervention group, (table 9). The Kaplan-Meier curves below (fig. 12) show the survival trends of patients post re-operations, minor amputations and major amputations. Patients survival is highest when they had minor amputation and open revascularization compared to endovascular intervention and hybrid procedure. This may be due to the fact that, open surgery is more durable and coupled with minor amputation, patients are more likely to have uneventful post-operative recovery, regain ambulatory function and be restored to their former lifestyles.

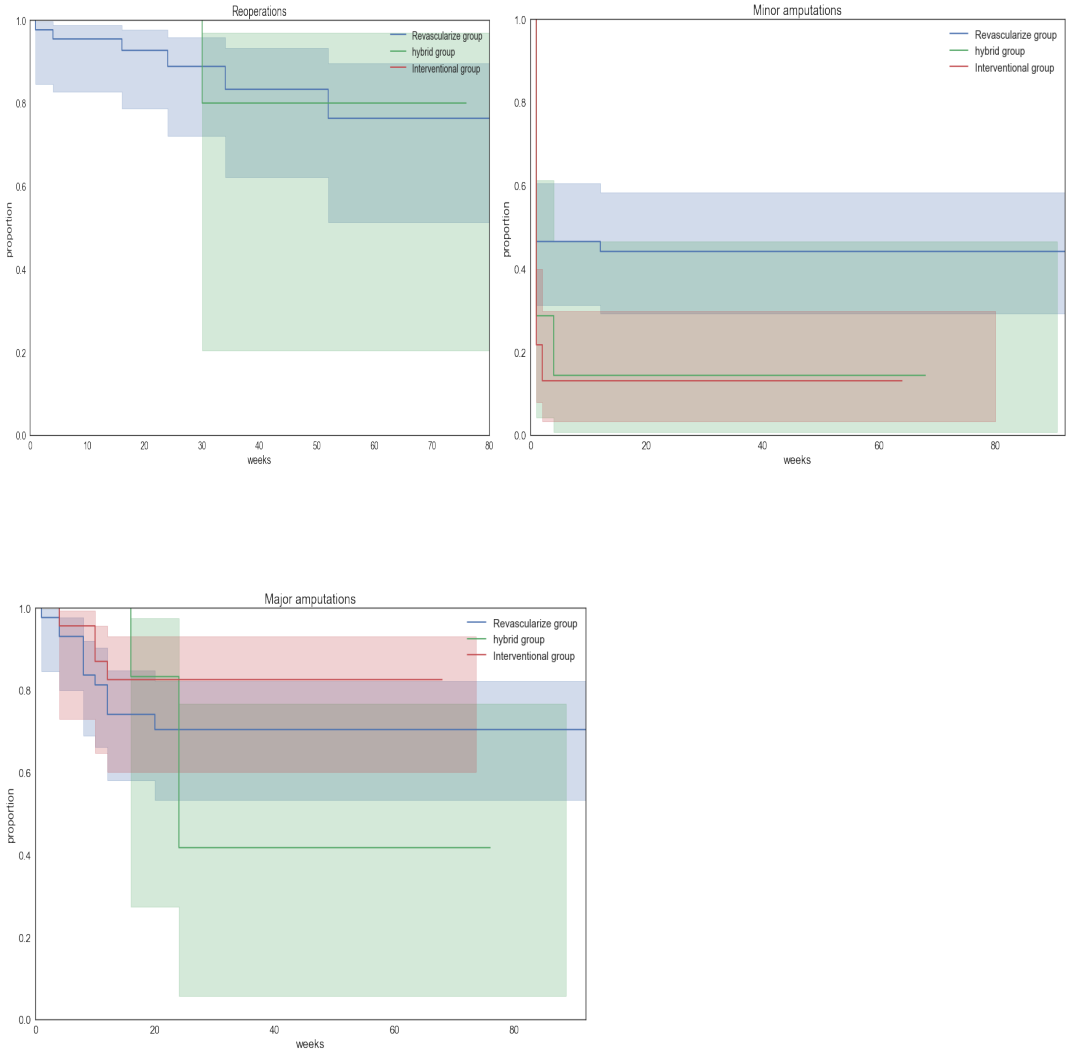

Fig. 12 Survival trend post-operative (Kaplan-Meier curve)

There was no peri-operative or 30- day mortality in our study, same as in the publication by Ambler et al, (21) but different from findings in many other studies, (25),(2),(21). At the end of one year follow up, six (8.2%) patients had died (one patient from urosepsis following inadvertent right ureteric injury, another patient from intestinal failure secondary to chronic mesenteric ischaemia and the remaining four deaths from unconfirmed causes). Majority of the mortality recorded (66.7%) occurred in patients with tissue loss, (28). One year amputation-free survival (AFS), defined as freedom from major amputation and all-cause mortality was 69.9% in our study.

The mean length of hospital stay (LOS) was 17 days in our study. This is comparable to the findings in a study in Germany (using data from the largest public health insurance in Germany) where the length of hospital stay varied from 11days to 22.1 days for Rutherford 4 to 6 disease, (28) and also in the study by Gibbons et al. (18) but higher than in some other reports, (38), (22).

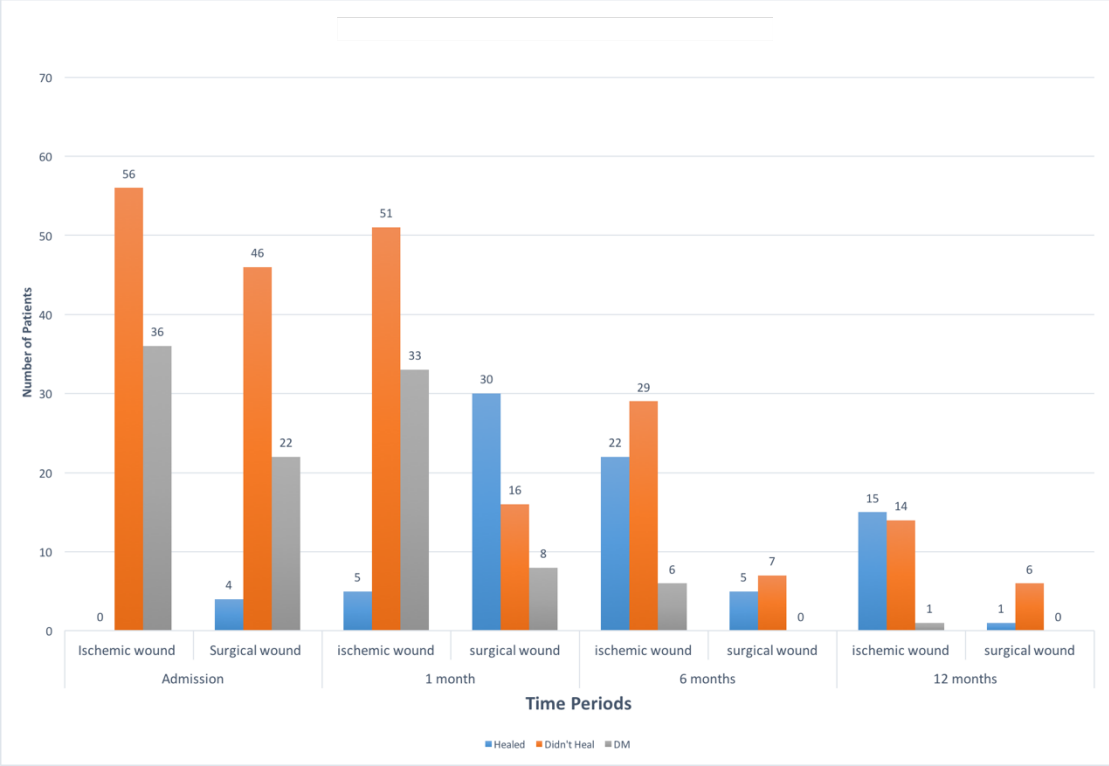

Fig. 13 Pattern of ischaemic and surgical wound healing post-operative

Association between metabolic profile and post-operative outcome

We do have enough evidence to accept the null hypothesis. Therefore, we can conclude that there is no association between all metabolic profiles measured at baseline of the study (BMI, WHR, TSFT, MAUC, Hb, fasting plasma glucose, HbA1c) and outcomes of ischaemic wound healing and ambulatory recovery at 6 months among the patients followed with lower limbs ischemia. Tables 10a and 10b show that all the odd ratios, p-values and 95% confidence intervals are not statistically significant. We do acknowledge that this preliminary study report has a small sample size.

Demographic characteristics and patient comorbidities were not included in the model for determination of association. This pilot study has provided many invaluable lessons which we hope to apply in a much larger prospective study to be conducted at this institution. A more robust multivariate analysis will be conducted with this much larger study with early, 5 year and 10-year follow-up data.

CONCLUSION

Demographics, co-morbidities, and procedural details of our study population reflected a relatively younger population with CLI. The rest of the profiles of patients depicted in this study is that of heavy smoking, abdominal obesity, overweight and high prevalence of hypertension. The post-operative outcomes in our study are similar to existing literature. Pre-operative ambulatory status is a predictor of post-operative ambulatory recovery. Diabetes is associated with more local wound complications and higher risk of major amputation. The rest of the metabolic profile factors did not reach statistical significance in predicting post-operative outcome. This may be due to a small sample size and short follow-up period.

LIMITATIONS

1. Small sample size
2. No validation of tools used for the anthropometric measurements
3. Lack of blinding of outcome assessors

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Appendix 1: Patient consent form

Consent Form for Participation in a Research Study (023/2016)

Name of Researcher(s)
Dr. Nadraj Naidoo (Principal Investigator) **Email:** nadraj.naidoo@uct.ac.za **Cell:**083 262 8651 E22 Vascular Lab Groote Schuur Hospital Ext 3324 **Dr. LILY WU** (Co-Investigator) **Email:** wxxlil001@myuct.ac.za **Cell:**072 958 7650
Title of study
Metabolic profile and post-operative outcomes in contemporary patients with peripheral arterial disease and critical limb ischaemia

Please read and complete this form carefully. If you are willing to participate in this study, ***circle*** the appropriate responses and sign and date the declaration at the end. If you do not understand anything and would like more information, please ask *me (Dr. LILY WU)*.

- I have had the research satisfactorily explained to me in verbal and / or written form (Synopsis) by the researcher. YES / NO

- I understand that the research will involve review of my clinical records with collection of information relating to the treatment ***of*** my ***illness***. As part of routine clinical follow-up *for* ***two years***, I ***may*** undergo an ultra-sound/CT scan and the results will be used as part of the study. YES / NO

- I understand that I may ***decide not to take part in this study or may*** withdraw from this study at any time without having to give an explanation. This will not affect my care or treatment. YES / NO

- I understand that all information about me will be treated in strict confidence. ***My identity will be protected by replacing my name with a code*** and that I will not be named in any written work arising from this study. YES / NO

- I understand that you will be discussing the progress of your research with others at Groote Schuur Hospital/University of Cape Town. YES / NO

I freely give my consent to participate in this research and have been given a copy of this form for my own information.

Name of Participant	Signature	Date
Name of Researcher	Signature	Date

You may contact the Human Research Ethics Committee if you have any ethical concerns or questions about your rights or welfare as a participant in this research. Kindly find contact details below.

Human Research Ethics Committee
Room E52 – 24 Old Main Building
Groote Schuur Hospital
Observatory
7925

Tel: (021) 406 6492
Facsimile: (021) 406 6411
Email: sumayah.ariefdien@uct.ac,za
Website: www.health.uct.ac.za/fhs/research/humanethics

Appendix 2: Data collection sheet

Metabolic profile and post-operative outcomes in contemporary patients with peripheral arterial disease and critical limb ischaemia

Appendix 2a:

Baseline Information

(Encircle relevant)

Baseline data

Attach Patient Sticker

Leg affected (State the side affected) ☐

Age ☐

Sex Male Female

Race Asian Black Coloured White

Phone number Home

Mobile

Next-of-kin

Date of admission

Clinical Data

Risk Factors

Hypertension Yes No

Diabetes Mellitus Yes No

Type 1 Type 2

On insulin or oral hypoglycaemic agent *or both*

Dyslipidaemia Yes No

Smoking history Smoker Ex-Smoker Non-smoker

Cardiovascular disease Yes No

Angina MI CCF Other

Renal disease (CKD) Yes No

Cerebrovascular Yes No

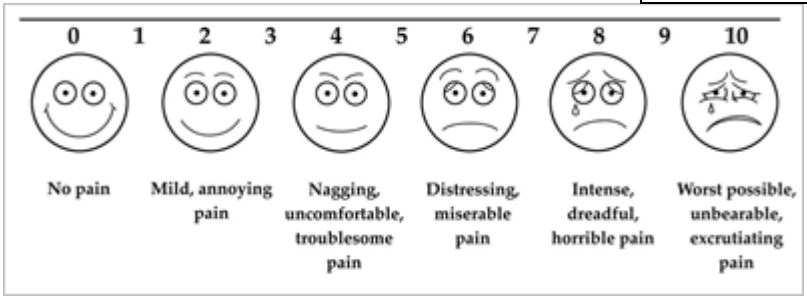
Stroke TIA

Rutherford Category 4 5 6

Rest Pain Minor Tissue Loss Major Tissue Loss

If Rutherford Category 4,

Visual analogue score ☐



If Rutherford Category 5 or 6,

Duration of ischaemic wounds ☐

Previous Peripheral Arterial Disease Intervention on the same leg

Yes No

Activity of daily living (ADL)

Ambulant Yes No

Independent Yes No

Active Yes No

Quality of life (VascuQoL-6) score ☐

Medication **Anticoagulation/antiplatelet** Yes No

Anti-hypertension Yes No

Number of agents ☐

Physical Data

Temperature

Heart Rate

Blood Pressure

Height

Weight

BMI

Waist circumference (*midpoint between the lower* margin of the *least palpable rib and the top of the iliac crest, at the end of expiration)*

Hip circumference (*Widest portion of the buttocks*)

WHR

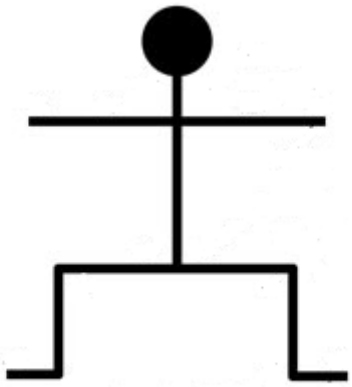
Does abdominal skin fold/apron hang over the groin (*by visual inspection) with patient in supine position*? Yes No

Mid-arm circumference

Triceps skin fold thickness

Level of disease

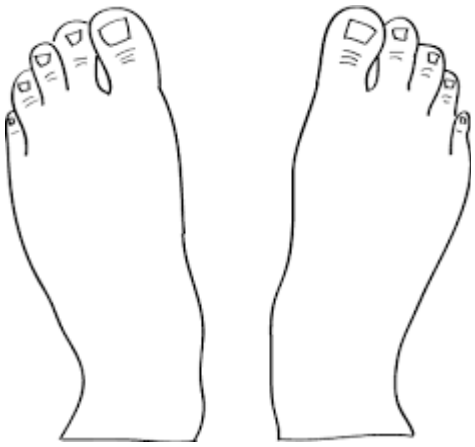
Aorto-iliac Femoral-popliteal Tibio-peroneal

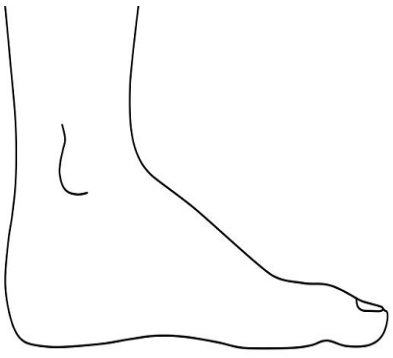


Buerger's test Positive Negative

Tissue loss Yes No

(Draw location and size)





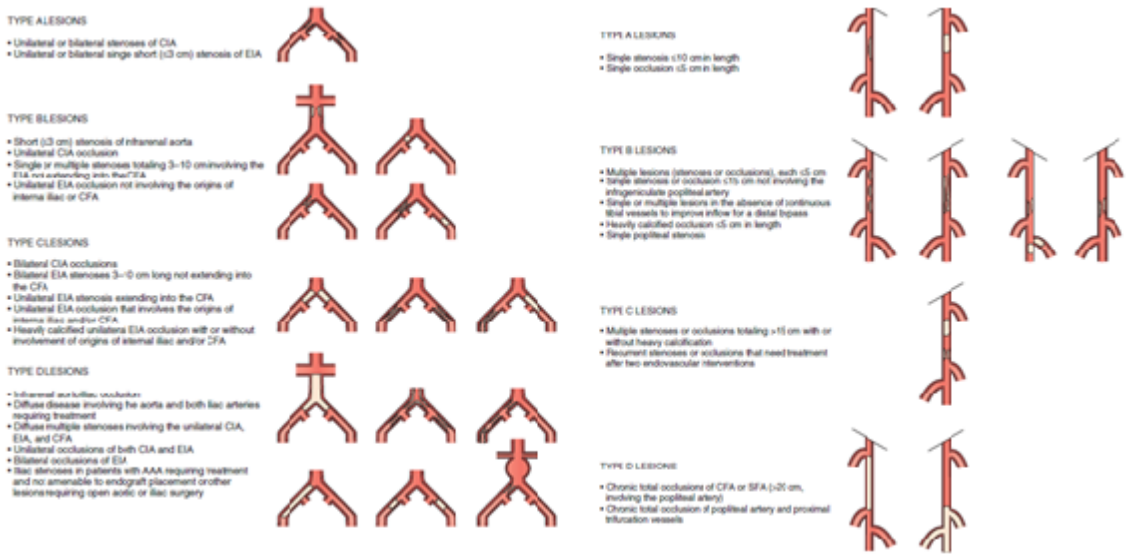
Laboratory Data

Haemoglobin	
White Blood Cell	
Platelets	
Creatinine	
INR	
Albumin	
Fasting cholesterol	
Fasting glucose	
HbA1C	

Ankle pressures	DP	
	PT	

Ankle brachial index	

TASC grading of main lesion (Encircle relevant)



Ultrasound measure of depth of skin to CFA in the relevant groin ☐

Duplex	Yes	No
CT Angiogram	Yes	No
Digital subtraction angiography (DSA)	Yes	No

Number of run-off vessels ☐

Weighting of Runoff Arteries

Site of Intervention	No. of Units Assigned*			
	3		2	1
CIA			EIA	IIA
EIA	CFA	or	SFA	PROF
CFA			SFA	PROF
SFA, POP				AT, PT, PER
AT			Distal tibial	Pedal arch
PT			Distal tibial	Pedal arch
PER			Pedal arch	Collaterals to AT and PT
DP	Pedal arch			

Note.—Modified with permission from reference 18.
CIA = common iliac artery, EIA = external iliac artery, IIA = internal iliac artery, CFA = common femoral artery, SFA = superficial femoral artery, POP = popliteal, PROF = profunda femoral artery, AT = anterior tibial artery, PT = posterior tibial artery, PER = peroneal artery, DP = dorsalis pedis artery.
*Points assigned for degree of occlusion: 3 = occluded throughout most of its length; 2.5 = occluded for less than half its length with visible collaterals; 2 = 50%–99% stenosed; 1 = 20%–49% stenosed; 0 = normal or minimal evidence of disease (ie, less than 20% narrowing).

Appendix 2b:

Intervention Data Capture Sheet

Attach Patient Sticker

Date of intervention ☐

Open bypass

Graft used	Vein	Prosthesis	
Prosthesis used	Dacron	PTFE	
Vein used	RSVG	NRSVG	
Spliced vein	Arm	GSV	Arm + GSV

Proximal anastomosis ☐

Distal anastomosis ☐

Technical success Yes No

Endovascular

Site CIA EIA CFA SFA Popliteal ATA Peroneal artery PTA

Angioplasty	Yes	No
Stent	Yes	No

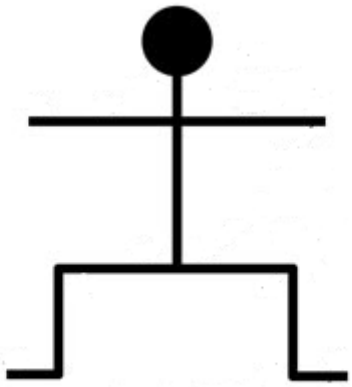
Technical Success Yes No

Hybrid (Combination of open and endovascular intervention)

Post-intervention

Outcome *Death* Failure Success

Physical examination – Pulse status post- intervention (mark relevant)



Ankle pressures DP

PT

Ankle brachial index

Duplex post-intervention Yes No

CT Angiogram post-intervention Yes No

DSA post-intervention Yes No

Graft patent Yes No

Appendix 2c:

Discharge Data Capture Sheet

Attach Patient Sticker

Date of discharge

Outcome/ Mortality

Alive Dead

Amputation Nil Toe TMA SMA BKA AKA

Time from initial intervention to amputation:

Any re-operation on the limb Yes No

Specify if yes:

Morbidity (If yes, please encircle relevant one in following list)

Incisional wound/Puncture Site complications Yes No

Bleeding

Haematoma

Local wound infection

Seroma

Gaped wound

False aneurysm

Graft/Endo-vascular Yes No

Occlusion

Graft sepsis

If yes time of occurrence after operation (DURATION) ☐

Cardiac Yes No

(Myocardial infarction, acute coronary syndrome, arrhythmia)

Neurological Yes No

(Stroke, transient ischaemic attack (TIA), amaurosis fugax)

Lung Yes No

(Infection, pneumonia, pulmonary embolism, pneumothorax, requirement for ventilation, tracheostomy)

Leg Yes No

(DVT, cellulitis)

Urological Yes No

(Urinary retention, urine infection, ARF)

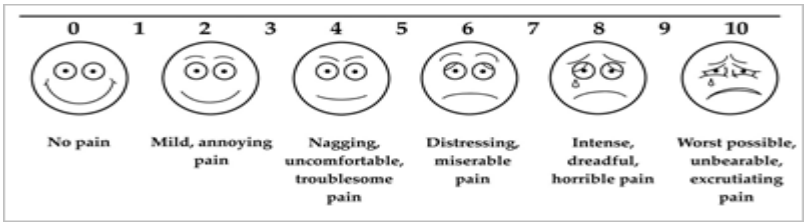
Bowel Yes No

(Bleeding, obstruction, ischaemia)

Rest pain if Category 4 Rutherford

Relief of rest pain Yes No

Visual analogue score



Wound healing if Category 5&6 Rutherford

Ischaemic wounds Healed

Present

If healed, specify when wound(s) healed:

Surgical wounds Healed

Present

If healed, specify when wound(s) healed:

Appendix 2d:

Follow-up data capture sheet

Attach Patient Sticker

Intervention (state the surgical intervention patient had)

Duration since intervention

Outcome Alive *Dead*

Amputation Nil Toe TMA SMA BKA AKA

Time from initial intervention to amputation:

Any re-operation on the limb since last visit Yes No

Specify if yes:

Time from initial intervention to re-operation:

Acute Coronary Syndrome since last visit Yes No

Stroke/TIA since last visit Yes No

Re-admission since last visit Yes No

Date of re-admission

Specify reason if yes:

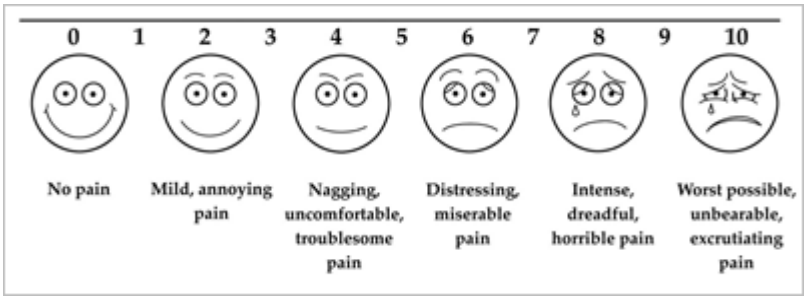
Ambulatory Status Ambulant Non-ambulant

Quality of life (VascuQoL-6) score ☐

Rest pain if Category 4 Rutherford

Relief of rest pain Yes No

Visual analogue score ☐



Wound healing if Category 5&6 Rutherford

Ischaemic wounds Healed
Present

If healed, specify when wound(s) healed:

Surgical wounds Healed
Present

If healed, specify when wound(s) healed:

Ankle pressures DP PT ☐ ☐

Ankle brachial index ☐

Duplex Yes No

CT Angiogram Yes No

Digital subtraction angiography (DSA) Yes No

If previous angioplasty, Need for further intervention? Yes No

If previous vein graft,

Primary graft patency	Yes	No
Assisted primary patency	Yes	No
Secondary graft patency	Yes	No
Need for further intervention	Yes	No

If previous prosthetic graft,

Primary graft patency	Yes	No
Secondary graft patency	Yes	No
Need for further intervention	Yes	No

Appendix 3: Departmental Research Committee approval

UNIVERSITY OF CAPE TOWN

Department of Surgery

Departmental Research Committee
Dr Timothy Pennel
3rd Floor, Christiaan Barnard Building, Medical School
Anzio Road, Observatory 7925, South Africa
Tel (021) 406 6476
Email: tim.pennel@uct.ac.za
Email: warda.brown@uct.ac.za

Dr L Wu
Department of Surgery
Division of General Surgery
Groote Schuur Hospital
University of Cape Town

Dear Dr Wu,

RE: PROJECT 2015/055

PROJECT TITLE: **Metabolic profile and post-operative outcome amongst patients with critical limb Ischamia**

The above proposal was reviewed by the Department of Surgery Research Committee and I am pleased to inform you that the committee approved the study.

Please use the above project number in all future correspondence.

Yours sincerely

Signed

DR T PENNEL
CHAIRMAN: RESEARCH COMMITTEE

"OUR MISSION is to be an outstanding teaching and research university, educating for life and addressing the challenges facing our society."

Appendix 4: Human Research Ethics Committee approval

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E52-24 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6626
Email: shuretta.thomas@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

03 May 2016

HREC REF: 023/2016

Dr NG Naidoo
Vascular Lab
E22, NGSH

Dear Dr Naidoo

PROJECT TITLE: ***METABOLIC PROFILE AND POST-OPERATIVE OUTCOMES IN CONTEMPORARY PATIENTS WITH PERIPHERAL ARTERIAL DISEASE AND CRITICAL LIMB ISCHAEMIA (MPhil-candidate- Dr L Wu)***

Thank you for your letter to the Faculty of Health Sciences Human Research Ethics Committee dated 18 April 2016.

The HREC have **noted and approved** the updated informed consent form for the above-mentioned study.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please quote the HREC REF in all your correspondence.

Yours sincerely

Signed

PP **PROFESSOR MARC BLOCKMAN**
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS

Appendix 5: Patient information document

Patient Information Document

Participation in the following study

Metabolic profile and post-operative outcomes in contemporary patients with peripheral arterial disease and critical limb ischaemia

My name is LILY WU, a fellow in the Vascular Unit of Groote Schuur Hospital. I am conducting the above research in collaboration with the vascular unit as part of the requirements for my training for an MPhil in Vascular surgery.

Purpose of the research

Critical limb ischaemia is when you have pain in your leg with a non-healing wound or gangrene ***(a portion of the leg/foot dies)*** because of lack of blood flow to your leg. This study is to investigate any association between the ***nutritional status*** (metabolic profile) of adult patients with critical limb ischaemia and their post-operative outcomes. ***Some of the measurements and laboratory tests to be used in assessing the nutritional status/ metabolic profile include body weight, height, BMI, hemoglobin level, blood protein/ albumin level etc.***

Research data on this subject is scanty locally. Besides, this specific topic has not been comprehensively studied worldwide. Findings from this study may influence patient selection with respect to expected outcomes. It may also inform policy change regarding pre-operative patient optimization for surgery and thereby minimize post-operative morbidity and mortality.

Participant selection

All patients above 18 years with critical limb ischaemia who are treated in this hospital over a 2-year period will be kindly invited to take part in this study by willfully signing a consent form whiles on admission at the Vascular Ward (F16). We therefor invite you to take part in this study.

Voluntary Participation (Right to Refuse or Withdraw)

Your participation in this research is entirely voluntary. It is your choice whether to participate or not. Whether you choose to participate or not, ***you will receive the same treatment that you require for your sickness. In other words, if you decide not to take part in this study, that decision will not negatively affect your treatment.*** You may ***also*** change your mind later and ***withdraw your participation in this study*** even if you agreed earlier. Deciding later to stop participating in this study will ***also*** not negatively affect your treatment.

Procedures and Protocol

During the research ***period (2years)***, information about yourself, certain physical measurements (***body weight, height, BMI)***, the ***operation*** you will undergo and any ***complications*** that may ***occur*** will be ***recorded***. ***You are not compelled to give your consent to take part in this study.*** Before you decide, you can talk to anyone you feel comfortable with about the research. You are more than welcome to stop me as I go through the information document to explain to you any word(s) that you may not understand. If you have questions later, you can ask me or the other staff on the ward.

After the operation, ***you will be required to visit the clinic on a number of occasions (follow up)*** as part of ***our usual*** appointment ***schedule for patients treated for the same kind of illness as you have. There will be no additional clinic visit due to participation in this research. This will be*** at 1, 3 and six months, and at 1 and 2 years and further information will be ***recorded*** during that time ***concerning how well your wounds are healing or otherwise***. ***Any limb amputation or death will also be recorded.***

Should you not be able to make it to the clinic, we will reach you telephonically to follow up. Each call will last about 5 minutes.

Risks and Side Effects

This research only observes what happens to the patients with critical limb ischaemia. There is no use of a trial drug or device or new surgical technique. ***Therefore, there is nothing new that will be done to you in this research that may be a threat to your limb or life.***

Confidentiality

We will not disclose the identity of ***participants*** in ***this*** research. The information that we collect will be kept confidential***. You will be assigned a special code. The code will be used in place of your name for the purposes of this research***. Information collected during the research will be put away in a secure facility and only the researchers will ***have access to*** it. We will lock that information up with a lock and key. It will not be shared with or given to anyone ***else besides the researchers***.

Sharing the Results

The knowledge that we get from doing this research will be shared with you before it is made available to the public. Confidential information will not be shared. We will publish the results in order that other interested persons may learn from our research.

Who to Contact

If you have any questions you may ask them now or later, even after the study has started. If you wish to ask questions later, you may contact me via any of the following: Lily Wu, telephone # 072 958 7650, speed dial 77337, email wxxlil001@myuct.ac.za.

This proposal has been reviewed and approved by department of Surgery Research Ethics Committee at Groote Schuur Hospital, which is a committee responsible for making sure that research participants are protected from harm.

Appendix 6: WHO categorization of BMI

Classification of obesity - Wikipedia

https://en.wikipedia.org/wiki/Classification_of_obesity

BMI (kg/m^2)	Classification
< 18.5	underweight
18.5–24.9	normal weight
25.0–29.9	overweight
≥30.0	obesity

Appendix 7: WHO definition of abdominal obesity, TSFT, MUAC

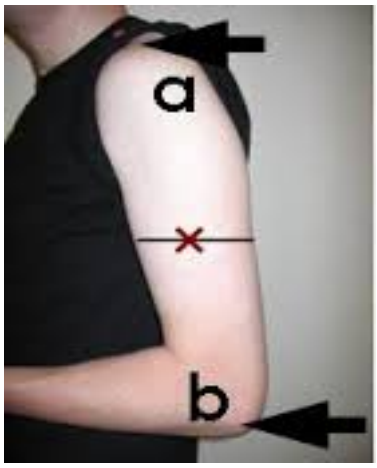
WHO cut-off points and risk of metabolic complications: (Waist circumference and waist–hip ratio, Report of a WHO expert consultation, Geneva, 8-11 December 2008)

Indicator	Cut-off points (abdominal obesity)		Risk of metabolic complications
Waist circumference	>94 cm (M);	>80 cm (W)	Increased
Waist circumference	>102 cm (M);	>88 cm (W)	Substantially increased
Waist–hip ratio	≥0.90 cm (M);	≥0.85 cm (W)	Substantially increased

M, men; W, women

Indicator	Anthropometric measurements		
	Gender	Normal values	Values showing malnutrition
	Male	11–12.5 mm	7.5–11 mm
Triceps skinfold thickness (TSFT)	Female	15–16.5 mm	10–15 mm
Mid upper arm circumference (MUAC)	Male	26–29.0 cm	20–26 cm
	Female	26–28.5 cm	20–26 cm

Appendix 8: Demonstration of how to measure MUAC



www.webmd.com › Diabetes › Guide

Appendix 9: Normal ranges of haematological and biochemical parameters

Parameters	**Normal range/ values**	**Our reference range**
Haemoglobin (g/dL)	13.5-17.5 (Male) 12.0-15.5 (Female)	MayoClinic.org
White cell count (x10^9/L)	3.5-10.5	MayoClinic.org
Platelet count (x10^9/L)	150-450	MayoClinic.org
INR	</=1.1	MayoClinic.org
Serum creatinine (umol/L)	74.3 - 107	MayoClinic.org
Serum albumin (g/dL)	3.5 - 5.0	Clinical Methods: The History, Physical, and Laboratory Examinations. 3rd edition
Fasting plasma glucose (mmol/L)	≥ 7.0	Definition and diagnosis of diabetes mellitus and intermediate hyperglycaemia. Report of a WHO/IDF Consultation
HbA1c	<5.7%	www.webmd.com › Diabetes › Guide